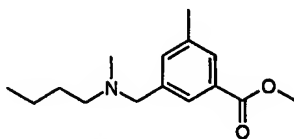


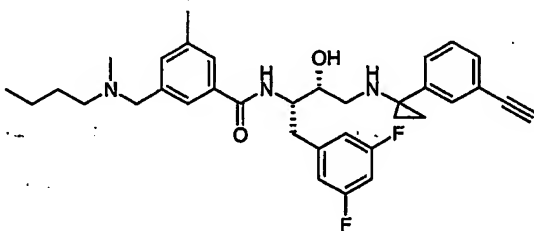
Methyl 3-([butyl(methyl)amino]methyl)-5-methylbenzoate



To methyl 3-(hydroxymethyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-177 (1.1 g, 6.1 mmol), in anhydrous
 5 methylene chloride (10 mL) is added methanesulfonyl chloride (663 μ L, 8.6 mmol) at -30°C , and the reaction is warmed to 0°C . The reaction stirred 1 h, then filtered. The filtrate is added to *N*-methylbutylamine (2.1 mL, 18.3 mmol), and the reaction stirred at room temperature 16 h. The solution is
 10 concentrated under reduced pressure. Purification by flash chromatography affords the title compound in pure form. ESI MS m/z 250.2 $[\text{M} + \text{H}]^{+}$.

Step 2

15 3-([Butyl(methyl)amino]methyl)-*N*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-5-methylbenzamide dihydrochloride



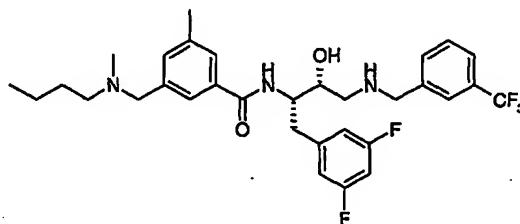
2 HCl

Methyl 3-([butyl(methyl)amino]methyl)-5-methylbenzoate
 20 (122 mg, 0.49 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (41 mg, 1 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and
 25 diisopropylethylamine (350 μ L, 2 mmol), HATU (240 mg, 0.63 mmol), and (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-([1-(3-ethynylphenyl)cyclopropyl]amino)butan-2-ol dihydrochloride

prepared by the method in EXAMPLE SP-272 (215 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 574.3 $[M + H]^+$.

EXAMPLE SP-189

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-5-methylbenzamide dihydrochloride



2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (112 mg, 0.45 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (38 mg, 0.9 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350 μ L, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride

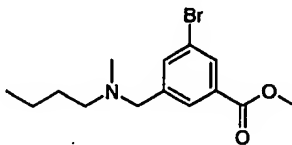
prepared by the method in EXAMPLE SP-272 (201 mg, 0.44 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 592.3 $[M + H]^+$.

EXAMPLE SP-190

3-Bromo-5-([butyl(methyl)amino]methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)benzamide dihydrochloride

Step 1

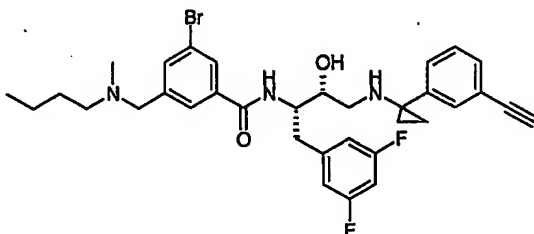
Methyl 3-bromo-5-([butyl(methyl)amino]methyl)benzoate



To a solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (4.1 g, 16.8 mmol) in anhydrous methylene chloride (35 mL) at -30 °C is added methanesulfonyl chloride (1.82 mL, 23.5 mmol) followed by triethylamine (4.7 mL, 33.6 mmol). The reaction mixture is stirred for 45 min at 0 °C, and then filtered. The filtrate is added to N-methylbutylamine (6 mL, 50.4 mmol) and stirred at room temperature for 16 h. The solution is concentrated under reduced pressure, and the residue is purified by flash column chromatography (silica, 8% ethyl acetate/hexanes) to give the title compound. ESI MS m/z 314.1 $[M + H]^+$.

Step 2

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride

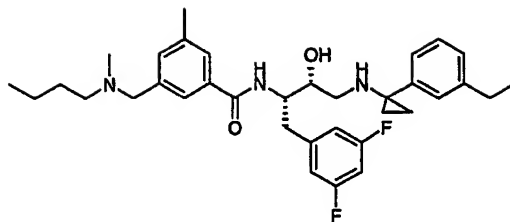


2 HCl

5 Methyl 3-bromo-5-([butyl(methyl)amino]methyl)benzoate (113 mg, 0.36 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (30 mg, 0.72 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced
10 pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (250 μ L, 1.44 mmol), HATU (170 mg, 0.45 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-([1-(3-ethynylphenyl)cyclopropyl]amino)-3-methylbutan-2-ol dihydrochloride prepared as in EXAMPLE SP-264 (170 mg, 0.4
15 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added.
20 The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 638.2 $[M + H]^+$.

EXAMPLE SP-191

3-([Butyl(methyl)amino]methyl)-N-((1S,2R)-1-(3,5-
25 difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methylbenzamide dihydrochloride

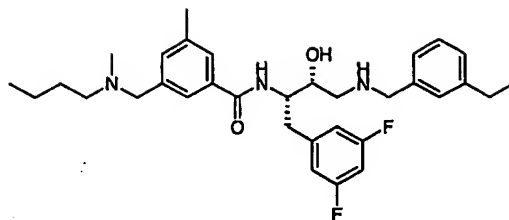


2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-
 {[butyl(methyl)amino]methyl}-5-methylbenzoate (132 mg, 0.53
 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4
 5 mL), and lithium hydroxide monohydrate is added (45 mg, 1.06
 mmol), and the reaction stirred 16 h. The solution is
 concentrated under reduced pressure. The residue is
 redissolved in DMF (5 mL), and diisopropylethylamine (350 μ L, 2
 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-
 10 difluorophenyl)-1-[[1-(3-ethylphenyl)cyclopropyl]amino]butan-
 2-ol prepared by the method in EXAMPLE SP-272 (191 mg, 0.5
 mmol) are added. The reaction stirred at room temperature 16
 h. The reaction mixture is diluted with ethyl acetate, washed
 with water, saturated sodium bicarbonate, brine, dried (sodium
 15 sulfate), filtered, and concentrated under reduced pressure.
 Purification by flash column chromatography (silica, 8%
 methanol/methylene chloride) provides the title compound as
 the free base. The residue is dissolved in diethyl ether (3
 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added.
 20 The mixture is concentrated under reduced pressure to yield
 the title compound. ESI MS m/z 578.4 $[M + H]^+$.

EXAMPLE SP-192

3-([Butyl(methyl)amino]methyl)-N-((1S,2R)-1-(3,5-
 25 difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-
 methylbenzamide dihydrochloride

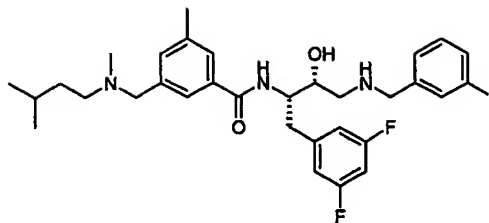


2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-
 {[butyl(methyl)amino]methyl}-5-methylbenzoate (122 mg, 0.49
 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4
 5 mL), and lithium hydroxide monohydrate is added (41 mg, 1.0
 mmol), and the reaction stirred 16 h. The solution is
 concentrated under reduced pressure. The residue is
 redissolved in DMF (5 mL), and diisopropylethylamine (350 μ L, 2
 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-
 10 difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol
 dihydrochloride prepared by the method in EXAMPLE SP-272 (203
 mg, 0.5 mmol) are added. The reaction stirred at room
 temperature 16 h. The reaction mixture is diluted with ethyl
 acetate, washed with water, saturated sodium bicarbonate,
 15 brine, dried (sodium sulfate), filtered, and concentrated
 under reduced pressure. Purification by flash column
 chromatography (silica, 8% methanol/methylene chloride)
 provides the title compound as the free base. The residue is
 dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in
 20 diethyl ether (1 mL) is added. The mixture is concentrated
 under reduced pressure to yield the title compound. ESI MS
 m/z 552.3 $[M + H]^+$.

EXAMPLE SP-193

25 N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-
 iodobenzyl)amino]propyl}-3-[[isopentyl(methyl)amino]methyl]-5-
 methylbenzamide dihydrochloride



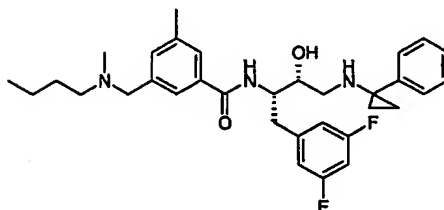
2 HCl

Analogous to the method described in EXAMPLE SP-184, 2 mL of the stock solution is added to a solution of *N*-isoamylmethylamine (526 μ L, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (42 mg, 1 mmol). The reaction is stirred 16 h and is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (355 μ L, 2 mmol), HATU (242 mg, 0.64 mmol), and (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (257 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 7% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1*N* hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 664.2 $[M + H]^+$.

EXAMPLE SP-194

3-[[Butyl(methyl)amino]methyl]-*N*-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-

phenylcyclopropyl) amino]propyl}-5-methylbenzamide
dihydrochloride



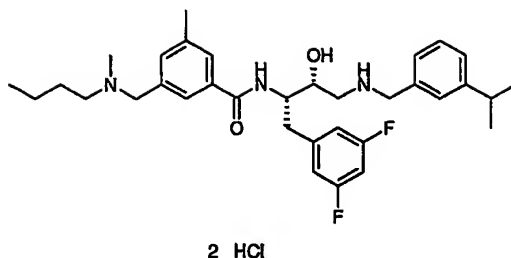
2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-
5 {[butyl(methyl)amino]methyl}-5-methylbenzoate (170 mg, 0.68
mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4
mL), and lithium hydroxide monohydrate is added (57 mg, 1.4
mmol), and the reaction stirred 2 h. The solution is
concentrated under reduced pressure. The residue is
10 redissolved in DMF (3 mL), and diisopropylethylamine (472 μ L,
2.7 mmol), HATU (322 mg, 0.85 mmol), and (2R,3S)-3-amino-4-
(3,5-difluorophenyl)-1-[(1-phenylcyclopropyl)amino]butan-2-ol
dihydrochloride prepared by the method in EXAMPLE S-XYZ (275
mg, 0.68 mmol) are added. The reaction stirred at room
15 temperature 16 h. The reaction mixture is diluted with ethyl
acetate, washed with water, saturated sodium bicarbonate,
brine, dried (sodium sulfate), filtered, and concentrated
under reduced pressure. Purification by flash column
chromatography (silica, 8% methanol/methylene chloride)
20 provides the title compound as the free base. The residue is
dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in
diethyl ether (1 mL) is added. The mixture is concentrated
under reduced pressure to yield the title compound. ESI MS
 m/z 550.3 $[M + H]^+$.

25

EXAMPLE SP-195

3-({[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-
difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl)-
5-methylbenzamide dihydrochloride

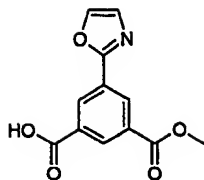


Analogous to the method in EXAMPLE SP-188, methyl 3-
 {[butyl(methyl)amino]methyl}-5-methylbenzoate (50 mg, 0.2
 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4
 5 mL), and lithium hydroxide monohydrate is added (17 mg, 0.4
 mmol), and the reaction stirred 16 h. The solution is
 concentrated under reduced pressure. The residue is
 redissolved in DMF (2 mL), and diisopropylethylamine (140 μ L,
 0.8 mmol), HATU (95 mg, 0.25 mmol), and (2R,3S)-3-amino-4-
 10 (3,5-difluorophenyl)-1-[(3-isopropylbenzyl)amino]butan-2-ol
 dihydrochloride prepared by the method in EXAMPLE SP-170, Step
 4 (85 mg, 0.2 mmol) are added. The reaction stirred at room
 temperature 16 h. The reaction mixture is diluted with ethyl
 acetate, washed with water, saturated sodium bicarbonate,
 15 brine, dried (sodium sulfate), filtered, and concentrated
 under reduced pressure. Purification by flash column
 chromatography (silica, 8% methanol/methylene chloride)
 provides the title compound as the free base. The residue is
 dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in
 20 diethyl ether (1 mL) is added. The mixture is concentrated
 under reduced pressure to yield the title compound. ESI MS
 m/z 566.3 $[M + H]^+$.

EXAMPLE SP-196

25 3-[[Butyl(methyl)amino]methyl]-N-((1S,2R)-1-(3,5-
 difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-
 hydroxypropyl)-5-(1,3-oxazol-2-yl)benzamide dihydrochloride
 Step 1

3-(Methoxycarbonyl)-5-(1,3-oxazol-2-yl)benzoic acid

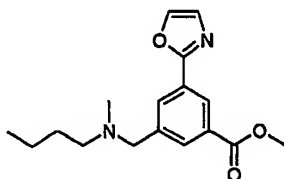


To a -70 °C stirred solution of oxazole (432 mg, 6.3 mmol) in tetrahydrofuran (10 mL) is added *n*-butyllithium (2.5 M in hexanes, 2.75 mL, 6.9 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 18.75 mL, 18.75 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of 3-iodo-5-(methoxycarbonyl)benzoic acid prepared by the method in EXAMPLE SP-281, step 1 (1.8 g, 6 mmol) in anhydrous tetrahydrofuran (10 mL) followed by palladium(0) tetrakis(triphenylphosphine) (291 mg, 0.25 mmol). The reaction mixture is heated at reflux for 15 h. The reaction mixture is cooled, filtered through diatomaceous earth, diluted with ethyl acetate (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% methanol/methylene chloride) provides the title compound in pure form. ESI MS *m/z* 246.1 [M - H]⁻.

20

Step 2

Methyl 3-{[butyl(methyl)amino]methyl}-5-(1,3-oxazol-2-yl)benzoate



25

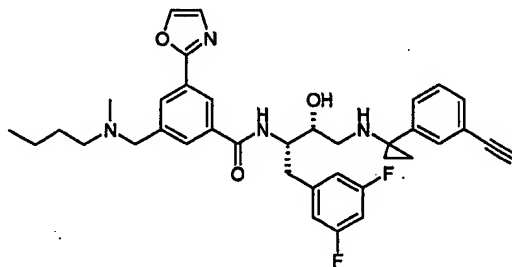
To an ice-cold solution of 3-(methoxycarbonyl)-5-(1,3-oxazol-2-yl)benzoic acid (340 mg, 1.4 mmol) in anhydrous tetrahydrofuran (10 mL) is added lithium borohydride (250 mg,

11 mmol) slowly. The reaction is stirred 30 min, then absolute ethanol (4 mL) is added, and the reaction is stirred 1 h. The solution is poured onto ice containing excess hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with water, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue is redissolved in 20% methanol/benzene (50 mL), and 2M trimethylsilyldiazomethane in hexane (0.9 mL, 1.8 mmol) is added. The reaction is stirred 2 h at room temperature, then concentrated under reduced pressure. The residue is redissolved in anhydrous methylene chloride (10 mL), cooled to -30 °C, then methanesulfonyl chloride (150 µL, 1.9 mmol) and triethylamine (380 µL, 2.7 mmol) are added. The reaction is stirred at 0 °C 15 min, then *N*-methylbutylamine (480 µL, 4 mmol) is added, and the reaction is stirred 16 h at room temperature. The solution is concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 40-100% ethyl acetate/hexane gradient) provides the title compound in pure form. ESI MS m/z 303.3 $[M + H]^+$.

20

Step 3

3-{[Butyl(methyl)amino]methyl}-*N*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)benzamide dihydrochloride



2 HCl

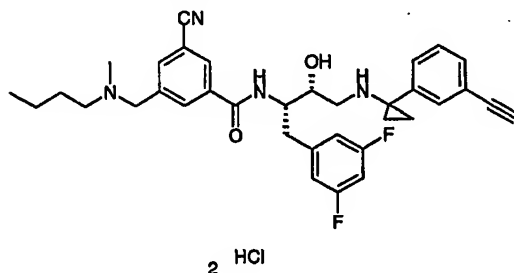
25

Methyl 3-{[butyl(methyl)amino]methyl}-5-(1,3-oxazol-2-yl)benzoate (30 mg, 0.1 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide

monohydrate is added (10 mg, 0.2 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (1 mL), and diisopropylethylamine (70 μ L, 0.4 mmol), HATU (57 mg, 0.15 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride (203 mg, 0.5 mmol) are added. The reaction stirred at room temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9-10% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 627.3 $[M + H]^+$.

EXAMPLE SP-197

3-{{[Butyl(methyl)amino]methyl}-5-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride



3-Bromo-5-(methoxycarbonyl)benzoic acid (4 g, 15.4 mmol) and copper(I) cyanide (4.1 g, 89.5 mmol) in N-methylpyrrolidinone (20 mL) is heated at 175 $^{\circ}$ C for 4 h. The reaction is cooled, and water is added. The aqueous solution is extracted with methylene chloride, washed with 1N hydrochloric acid (aq), brine, dried (sodium sulfate),

filtered, and concentrated under reduced pressure. The residue is dissolved in tetrahydrofuran (20 mL), cooled in an ice bath, and lithium borohydride (475 mg, 22 mmol) is added slowly. The reaction stirred at this temperature 2 h.
5 Absolute ethanol (4 mL) is added dropwise, and the reaction stirred 30 min. The mixture is poured on ice containing excess hydrochloric acid. After gas evolution ceases, the solution is extracted with methylene chloride and concentrated under reduced pressure.

10 The residue is dissolved in 20% methanol/benzene (20 mL), and 2M trimethylsilyldiazomethane in hexane (1.3 mL, 2.6 mmol) is added. The reaction stirred at room temperature 2 h and is concentrated under reduced pressure. The residue is then dissolved in anhydrous methylene chloride (10 mL), cooled to
15 -30 °C, then methanesulfonyl chloride (216 µL, 2.8 mmol) and triethylamine (556 µL, 4 mmol) are added. The reaction is warmed to 0 °C and stirred 15 min, then filtered. The filtrate is added to N-methylbutylamine (5 mL) and stirred 16 h. The solution is concentrated under reduced pressure and
20 purification by flash chromatography (silica gel, 40% ethyl acetate/hexane) gives an oil. The oil (107 mg) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (35 mg, 0.8 mmol), and the reaction stirred 1.5 h. The solution is concentrated under
25 reduced pressure.

The residue is redissolved in DMF (3 mL), and diisopropylethylamine (280 µL, 1.6 mmol), HATU (230 mg, 0.6 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[[1-(3-ethynylphenyl)cyclopropyl]amino]butan-2-ol dihydrochloride
30 (206 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column

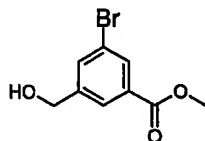
chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 585.3 $[M + H]^+$.

EXAMPLE SP-198

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2-furylmethyl(methyl)amino]methyl]-5-methylbenzamide dihydrochloride

Step 1

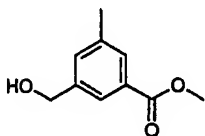
Methyl 3-bromo-5-(hydroxymethyl)benzoate



To an ice-cold, stirred solution of 3-bromo-5-(methoxycarbonyl)benzoic acid (5.0 g, 19.3 mmol) in tetrahydrofuran (77.2 mL) is added borane dimethyl sulfide complex (10.6 mL, 2.0 M tetrahydrofuran, 21.1 mmol). The reaction mixture is heated at 50 °C for 2 h. The reaction mixture is quenched with methanol (50 mL) and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) affords the title compound. ^1H NMR (300 MHz, CDCl_3) δ 8.03 (s, 1H), 7.90 (s, 1H), 7.69 (s, 1H), 4.69 (s, 1H), 3.91 (s, 3H), 2.83 (br s, 1H).

Step 2

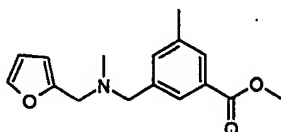
Methyl 3-(hydroxymethyl)-5-methylbenzoate



To a stirred solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (4.53 g, 18.5 mmol) in dioxane (74 mL) is added cesium carbonate (6.0 g, 18.5 mmol), potassium carbonate (5.1 g, 37 mmol), and palladium(0) tetrakis(triphenylphosphine) (2.1 g, 1.85 mmol), followed by trimethyl boroxine (5.1 mL, 37 mmol). The reaction mixture is refluxed for 12 h, cooled to room temperature, and then partitioned between water and ethyl acetate. The organic layer is washed with water and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The black oil is adsorbed onto silica gel followed by purification by flash column chromatography (silica, 25% ethyl acetate/hexanes) to provide the title compound. ¹H NMR (300 MHz, CDCl₃) δ 7.75 (s, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 5.31 (br s, 1H), 4.53 (s, 1H), 3.84 (s, 3H), 2.36 (s, 3H).

Step 3

Methyl 3-[[[(2-furylmethyl)(methyl)amino]methyl]-5-methylbenzoate



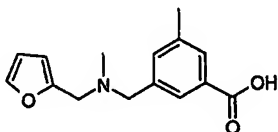
To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. N-Methylfurfurylamine (367 mg, 3.3 mmol) is added to the filtrate and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl

acetate/hexanes) provided the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, $J = 11$ Hz, 2H), 3.79 (d, $J = 6$ Hz, 2H), 6.32 (d, $J = 2$ Hz, 1H), 6.21 (d, $J = 3$ Hz, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 3.53 (s, 2H), 2.39 (s, 3H), 2.23 (s, 3H).

5

Step 4

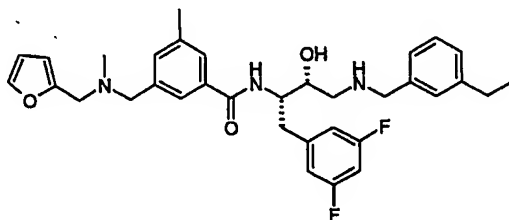
3-[[(2-Furylmethyl) (methyl) amino]methyl]-5-methylbenzoic acid



To a stirred solution of methyl 3-[[(2-furylmethyl) (methyl) amino]methyl]-5-methylbenzoate (180 mg, 0.66 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (277 mg, 6.6 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 258 $[\text{M} + \text{H}]^+$.

Step 5

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[[(2-furylmethyl) (methyl) amino]methyl]-5-methylbenzamide dihydrochloride



2 HCl

To a stirred solution of 3-[[(2-furylmethyl) (methyl) amino]methyl]-5-methylbenzoic acid (170 mg, 0.66 mmol) in methylene chloride (3 mL) is added HBTU (375 mg, 0.99 mmol), HOBT (134 mg, 0.99 mmol), and N,N -

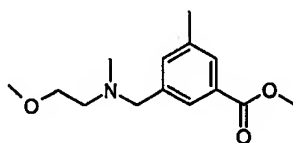
diisopropylethylamine (0.334 mL, 1.98 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (269 mg, 0.66 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords the title compound as the free base. The compound is dissolved in methanol (2 mL), and to this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol). The reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 576 $[M + H]^+$.

EXAMPLE SP-199

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[2-methoxyethyl(methyl)amino]methyl]-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-[[2-methoxyethyl(methyl)amino]methyl]-5-methylbenzoate

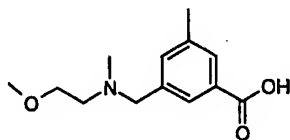


To an ice-cold stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. 2-Methoxy-N-methyleneamine (0.354 mL, 3.3 mmol) is

added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) provided the title compound. ¹H NMR (300 MHz, CDCl₃) δ, 7.75 (d, *J* = 5 Hz, 2H), 7.37 (s, 3H), 3.90 (s, 1H), 3.56 (s, 2H), 3.52 (t, *J* = 6 Hz, 2H), 3.34 (s, 3H), 2.61 (t, *J* = 6 Hz, 2H), 2.39 (s, 3H), 2.26 (s, 3H).

Step 2

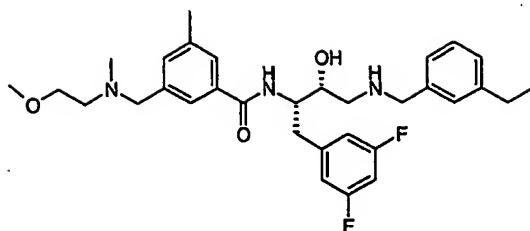
3-[[(2-Methoxyethyl) (methyl) amino] methyl]-5-methylbenzoic acid



To a stirred solution of methyl 3-[[(2-methoxyethyl) (methyl) amino] methyl]-5-methylbenzoate (180 mg, 0.72 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (302 mg, 7.2 mmol) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS *m/z* 238 [M + H]⁺.

Step 3

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[[(2-methoxyethyl) (methyl) amino] methyl]-5-methylbenzamide dihydrochloride



2 HCl

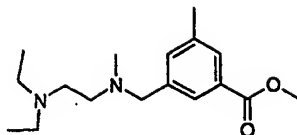
To a stirred solution of 3-[[2-methoxyethyl](methyl)amino]methyl]-5-methylbenzoic acid (140 mg, 0.56 mmol) in methylene chloride (3 mL) is added HBTU (318 mg, 0.84 mmol), HOBT (114 mg, 0.84 mmol), and *N,N*-diisopropylethylamine (0.284 mL, 1.68 mmol), followed by (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (228 mg, 0.56 mmol). The reaction mixture is stirred for 24 h at room temperature, diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords the title compound as the free base. The compound is dissolved in methanol (2 mL), and to this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol). The reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 554 $[M + H]^+$.

EXAMPLE SP-200

3-[[[2-(Diethylamino)ethyl](methyl)amino]methyl]-*N*-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide trihydrochloride

Step 1

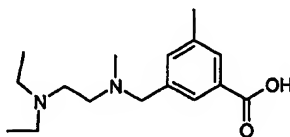
Methyl 3-[[[2-(diethylamino)ethyl](methyl)amino]methyl]-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.19 mmol) and triethylamine (241 mg, 2.38 mmol) in methylene chloride (5 mL) is added methanesulfonyl chloride (191 mg, 1.67 mmol). The reaction mixture is stirred for 15 min, the precipitate that formed is removed by filtration, and *N,N*-diethyl-*N'*-methylethylenediamine (465 mg, 3.57 mmol) was added. The reaction mixture is stirred at room temperature for 2 h and then concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gives the title compound. ¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 2H), 7.33 (s, 1H), 3.56 (s, 3H), 3.48 (s, 2H), 2.95 (m, 4H), 2.75 (m, 4H), 2.41 (s, 3H), 2.31 (s, 3H), 1.21 (m, 6H).

Step 2

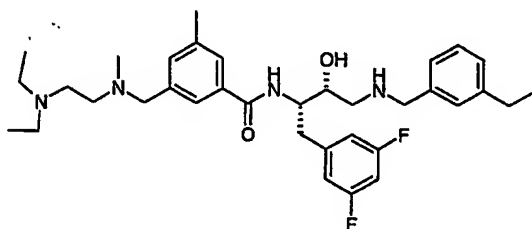
3-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoic acid



A mixture of methyl 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoate (296 mg, 1.01 mmol) and 3:1:1 methanol/tetrahydrofuran/2 N sodium hydroxide (10 mL) is stirred overnight and then partitioned between ethyl acetate and water. The aqueous layer is acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform. The aqueous layer is concentrated under reduced pressure to give the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.99 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 4.56 (m, 2H), 4.31 (m, 2H), 3.98 (m, 2H), 3.17 (m, 4H), 2.51 (s, 3H), 2.50 (s, 3H), 1.27 (m, 6H).

Step 3

3-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide trihydrochloride

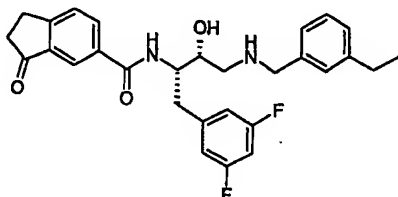


3 HCl

To a stirred solution of 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoic acid (267 mg, 0.959 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (391 mg, 0.959 mmol), HOBt (129 mg, 0.959 mmol), and *N,N*-diisopropylethylamine (496 mg, 3.84 mmol) in methylene chloride (5 mL) is added EDC (331 mg, 1.73 mmol). The reaction mixture is stirred overnight and then partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1:1 methylene chloride/methanol/ammonium hydroxide) gives the title compound. ESI MS m/z 595.4 $[M + H]^+$.

EXAMPLE SP-201

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxoindane-5-carboxamide

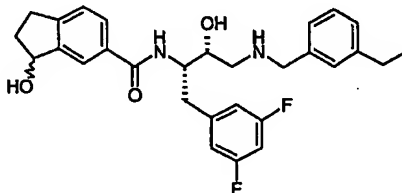


To 3-oxoindane-5-carboxylic acid (2.0 g, 11.5 mmol) in DMF (10 mL) is added diisopropylethylamine (8 mL, 46 mmol), HATU (5.5 g, 14.4 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol

5 dihydrochloride prepared by the method of EXAMPLE SP-272 (5.6 g, 13.8 mmol). The reaction is stirred 1 h at room temperature. The reaction was partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine,
10 dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) gives the title compound. ESI-MS m/z 493.2 $[M + H]^+$.

15 EXAMPLE SP-202

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxyindane-5-carboxamide



To an ice-cold solution of N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxoindane-5-carboxamide prepared by the method in EXAMPLE SP-201 (66 mg, 0.13 mmol) in methanol (3 mL) is added sodium borohydride (20 mg, 0.52 mmol). The reaction stirred at room temperature 3 h. The reaction is concentrated under reduced
25 pressure, redissolved in water (3 mL) and partitioned into ethyl acetate. The organic layer is washed with water, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS m/z 495.2 $[M + H]^+$.

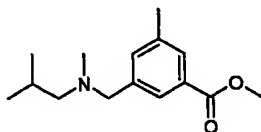
30

EXAMPLE SP-203

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[isobutyl(methyl)amino]methyl]-5-methylbenzamide hydrochloride

Step 1

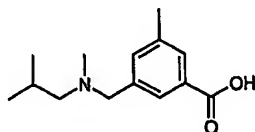
5 Methyl 3-[[isobutyl(methyl)amino]methyl]-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 10 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. N-Methylisobutylamine (287 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with 15 methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. ¹H NMR (300 MHz, 20 CDCl₃) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.36 (s, 1H), 3.90 (s, 3H), 3.44 (s, 2H), 2.38 (s, 3H), 2.14 (s, 3H), 2.10 (d, J = 8 Hz, 2H), 1.81 (m, 1H), 0.90 (d, J = 7 Hz, 6H).

Step 2

25 3-[[Isobutyl(methyl)amino]methyl]-5-methylbenzoic acid

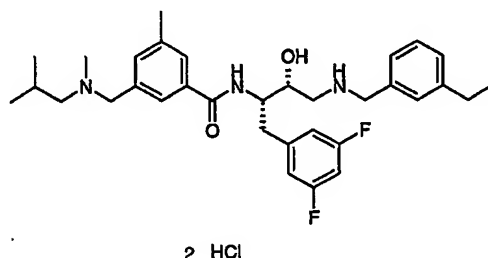


To a stirred solution of methyl 3-[[isobutyl(methyl)amino]methyl]-5-methylbenzoate (120 mg, 0.48 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 30 mL) is added lithium hydroxide (200 mg, 4.8 mmol), and the

reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 236 $[M + H]^+$.

Step 3

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-([isobutyl(methyl)amino]methyl)-5-methylbenzamide hydrochloride



To a stirred solution of 3-([isobutyl(methyl)amino]methyl)-5-methylbenzoic acid (110 mg, 0.48 mmol) in methylene chloride (3 mL) is added HBTU (273 mg, 0.72 mmol), HOBt (97 mg, 0.72 mmol), and *N,N*-diisopropylethylamine (0.243 mL, 1.44 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (196 mg, 0.48 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that

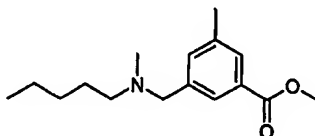
is formed is collected by filtration to provide the title compound. ESI MS m/z 552.5 $[M + H]^+$.

EXAMPLE SP-204

- 5 N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-
{[methyl(pentyl)amino]methyl}benzamide dihydrochloride

Step 1

Methyl 3-methyl-5-{[methyl(pentyl)amino]methyl}benzoate



10

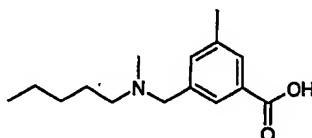
To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. N-Methylpentylamine (333 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.75 (d, J = 4 Hz, 2H), 7.36 (s, 1H), 3.90 (s, 3H), 3.47 (s, 2H), 3.13 (t, J = 9 Hz, 3H), 2.39 (s, 2H), 2.34 (d, J = 8 Hz, 2H), 2.18 (s, 3H), 1.45 (m, 5H), 1.32 (m, 2H).

20

25

Step 2

3-Methyl-5-{[methyl(pentyl)amino]methyl}benzoic acid



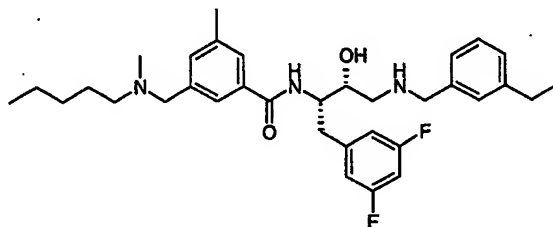
30

To a stirred solution of methyl 3-methyl-5-
{[methyl(pentyl)amino]methyl}benzoate (120 mg, 0.46 mmol) in
methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is
added lithium hydroxide (191 mg, 4.6 mmol), and the reaction
5 mixture stirred at room temperature for 2 h. The reaction
mixture is concentrated under reduced pressure, dissolved in
methylene chloride, filtered, and the filtrate concentrated
under reduced pressure to provide the title compound. ESI MS
 m/z 250 $[M + H]^+$.

10

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-
hydroxypropyl}-3-methyl-5-
{[methyl(pentyl)amino]methyl}benzamide dihydrochloride



2 HCl

15

To a stirred solution of 3-methyl-5-
{[methyl(pentyl)amino]methyl}benzoic acid (110 mg, 0.44 mmol)
in methylene chloride (3 mL) is added HBTU (250 mg, 0.66
mmol), HOBt (90 mg, 0.66 mmol), and *N,N*-diisopropylethylamine
20 (0.222 mL, 1.32 mmol), followed by (2R,3S)-3-amino-4-(3,5-
difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by
the method of EXAMPLE SP-272 (180 mg, 0.44 mmol), and the
reaction mixture is stirred for 12 h at room temperature. The
reaction mixture is diluted with methylene chloride, washed
25 with water, and saturated sodium bicarbonate, dried (magnesium
sulfate), filtered, and concentrated under reduced pressure.
Purification by flash column chromatography (silica, 10%
methanol/chloroform) affords a clear oil, which is dissolved
in methanol (2 mL). To this solution is added hydrochloric

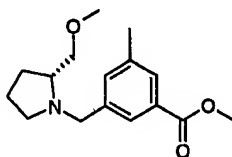
acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 566.5 $[M + H]^+$.

EXAMPLE SP-205

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzamide dihydrochloride

Step 1

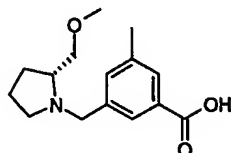
Methyl 3-[[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. (R)-2-(Methoxymethyl)pyrrolidine (380 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) provides the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 4.11 (d, J = 13 Hz, 1H), 3.90 (d, J = 6 Hz, 2H), 3.41 (m, 2H), 3.34 (m, 3H), 2.89 (m, 1H), 2.71 (m, 1H), 2.38 (s, 3H), 2.19 (m, 1H), 1.93 (m, 2H), 1.54 (m, 3H).

Step 2

3-{[(2R)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid

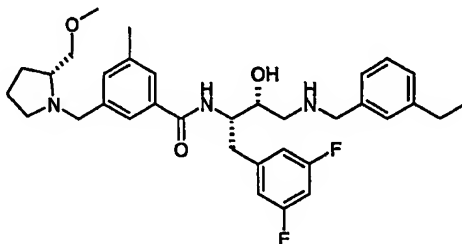


5 To a stirred solution of methyl 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate (120 mg, 0.43 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (180 mg, 4.3 mmol), and the reaction mixture stirred at room temperature for 2 h.

10 The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 264 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride



2 HCl

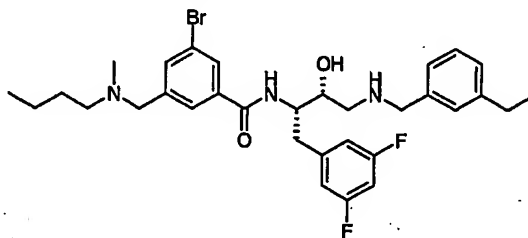
20 To a stirred solution of 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid (113 mg, 0.43 mmol) in methylene chloride (3 mL) is added HBTU (165 mg, 0.66 mmol), HOBT (89 mg, 0.66 mmol), and *N,N*-diisopropylethylamine (0.220 mL, 1.30 mmol), followed by

25 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE

SP-272 (175 mg, 0.43 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate),
 5 filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which was dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is
 10 stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 580.4 $[M + H]^+$.

15 EXAMPLE SP-206

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide dihydrochloride



2 HCl

20 Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate prepared by the method in EXAMPLE SP-190, Step 1 (170 mg, 0.54) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (45 mg, 1.1 mmol), and the reaction stirred 16 h. The solution is
 25 concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (375 μ L, 2.16 mmol), HATU (256 mg, 0.68 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (265

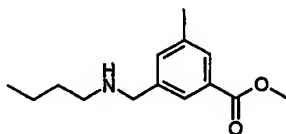
mg, 0.65 mmol) are added. The reaction stirred at room temperature 1 h. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 616.2 $[M + H]^+$.

EXAMPLE SP-207

3-[(Butylamino)methyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-[(butylamino)methyl]-5-methylbenzoate



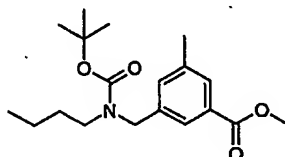
To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. Butylamine (0.543 mL, 5.5 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 89:10:1 chloroform/methanol/ammonium hydroxide) provides the title

compound. ^1H NMR (300 MHz, CDCl_3) δ 7.75 (s, 1H), 7.70 (s, 1H), 7.24 (br s, 1H), 4.42 (d, $J = 9$ Hz, 2H), 3.90 (s, 3H), 3.16 (m, 2H), 2.38 (s, 3H), 1.64 (s, 2H), 1.44 (m, 9H), 1.27 (m, 2H), 0.89 (t, $J = 7$ Hz, 3H).

5

Step 2

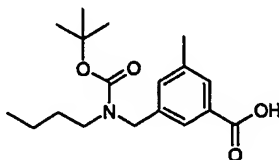
Methyl 3-[[[(tert-butoxycarbonyl)(butyl)amino]methyl]-5-methylbenzoate



10 To a stirred solution of methyl 3-[(butylamino)methyl]-5-methylbenzoate (70 mg, 0.30 mmol) in methylene chloride is added triethylamine (0.046 mL, 0.33 mmol), and 4-dimethylaminopyridine (4.0 mg, 0.03 mmol) followed by di-tert-butyl-dicarbonate (72 mg, 0.30 mmol). The reaction mixture is
15 stirred at room temperature for 24 h, diluted with methylene chloride, washed with 1 N hydrochloric acid, and brine. The organic solution is dried (magnesium sulfate), filtered, and concentrated under reduced pressure to afford the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.75 (s, 1H), 7.70 (s,
20 1H), 7.24 (br s, 1H), 4.42 (d, $J = 9$ Hz, 2H), 3.90 (s, 3H), 3.16 (m, 2H), 2.38 (s, 3H), 1.64 (s, 2H), 1.44 (m, 9H), 1.27 (m, 2H), 0.89 (t, $J = 7$ Hz, 3H).

Step 3

25 3-[[[(tert-Butoxycarbonyl)(butyl)amino]methyl]-5-methylbenzoic acid

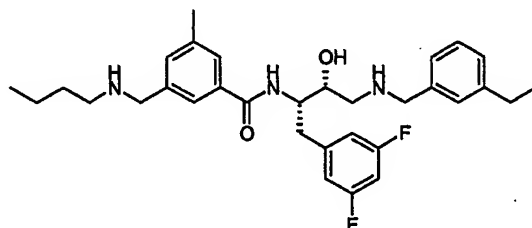


To a stirred solution of methyl 3-[[[(tert-butoxycarbonyl)(butyl)amino]methyl]-5-methylbenzoate (70 mg,

0.21 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (88 mg, 2.1 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound.

Step 4

3-[(Butylamino)methyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methylbenzamide dihydrochloride



2 HCl

To a stirred solution of 3-[[tert-butoxycarbonyl](butyl)amino]methyl]-5-methylbenzoic acid (90 mg, 0.28 mmol) in methylene chloride (3 mL) is added HBTU (160 mg, 0.42 mmol), HOBT (57 mg, 0.42 mmol), and *N,N*-diisopropylethylamine (0.142 mL, 0.84 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (114 mg, 0.28 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is

stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 538.5 $[M + H]^+$.

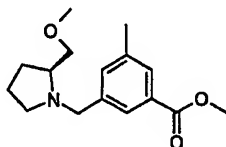
5

EXAMPLE SP-208

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzamide dihydrochloride

10 Step 1

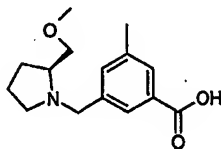
Methyl 3-[[2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-
15 (hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. (S)-(+)-2-(Methoxymethyl)pyrrolidine (380 mg, 3.3
20 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced
25 pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 4.12 (d, $J = 17$ Hz, 1H), 3.90 (s, 3H), 3.85 (m, 2H), 3.51 (m, 2H), 3.44 (m, 2H), 3.15 (s, 1H), 2.38 (s,
30 3H), 1.94 (m, 3H), 1.72 (m, 3H).

Step 2

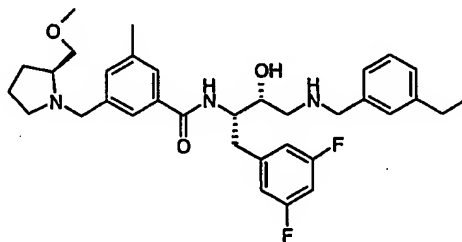
3-[[(2S)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzoic acid



To a stirred solution of methyl 3-[[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzoate (170 mg, 0.50 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (211 mg, 5.0 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 264 $[M + H]^+$.

Step 3

N-[(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzamide dihydrochloride



2 HCl

To a stirred solution of 3-[[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-5-methylbenzoic acid (110 mg, 0.42 mmol) in methylene chloride (3 mL) is added HBTU (240 mg, 0.63 mmol), HOBT (85 mg, 0.63 mmol), and *N,N*-diisopropylethylamine (0.212 mL, 1.26 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (171 mg, 0.42 mmol). The reaction mixture is stirred

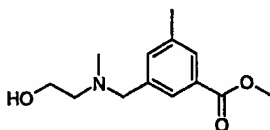
for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash
 5 column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl
 10 ether (10 mL). The precipitate that is formed was collected by filtration to provide the title compound. ESI MS m/z 580.4 $[M + H]^+$.

EXAMPLE SP-209

15 N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2-(2-hydroxyethyl)(methyl)amino]methyl]-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-[[2-(2-hydroxyethyl)(methyl)amino]methyl]-5-
 20 methylbenzoate

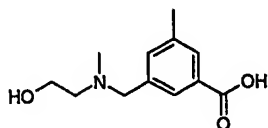


To an ice-cold stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5
 25 mmol). The reaction mixture is stirred for 15 min and filtered. 2-Methoxy-N-methyleneamine (0.354 mL, 3.3 mmol) is added to the filtrate and stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10
 30 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (50% ethyl acetate/hexanes) provides the title compound. ESI MS m/z 238 $[M + H]^+$.

Step 2

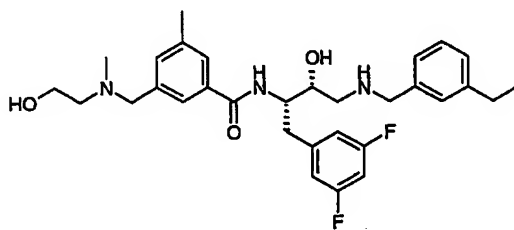
- 5 3-[[(2-Hydroxyethyl) (methyl) amino] methyl]-5-methylbenzoic acid



To a stirred solution of methyl 3-[[(2-hydroxyethyl) (methyl) amino] methyl]-5-methylbenzoate (180 mg, 0.72 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and
 10 water (1 mL) is added lithium hydroxide (302 mg, 7.2 mmol), and the reaction mixture is stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and concentrated under reduced pressure to provide the title
 15 compound. ESI MS m/z 224 $[M + H]^+$.

Step 3

- N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[[(2-hydroxyethyl) (methyl) amino] methyl]-5-methylbenzamide dihydrochloride
 20



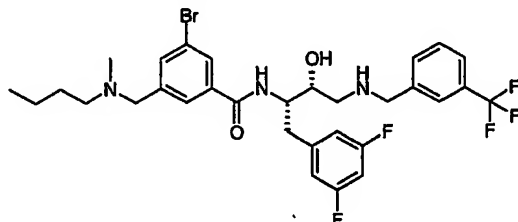
2 HCl

To a stirred solution of 3-[[(2-hydroxyethyl) (methyl) amino] methyl]-5-methylbenzoic acid (140 mg, 0.56 mmol) in methylene chloride (3 mL) is added HBTU (318
 25 mg, 0.84 mmol), HOBT (114 mg, 0.84 mmol), and *N,N*-diisopropylethylamine (0.284 mL, 1.68 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (228 mg, 0.56 mmol). The reaction mixture is stirred for 24 h at room temperature, diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this is added hydrochloric acid (5 mL of a 4 N solution in dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 540.4 $[M + H]^+$.

15 EXAMPLE SP-210

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)benzamide dihydrochloride



2 HCl

20 Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate prepared by the method in EXAMPLE SP-190, Step 1 (200 mg, 0.64) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (60 mg, 1.3 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (445 μ L, 2.6 mmol), HATU (304 mg, 0.8 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride

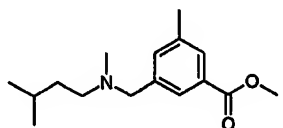
prepared by the method in EXAMPLE S-2511 (315 mg, 0.7 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, and saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 656.2 $[M + H]^+$.

EXAMPLE SP-211

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-{[isopentyl(methyl)amino]methyl}-5-methylbenzoate

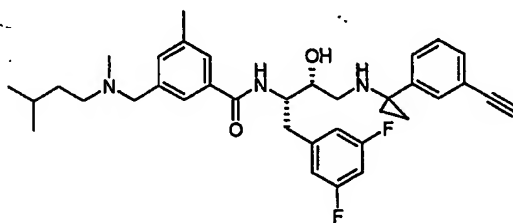


To methyl 3-(hydroxymethyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-198, Step 2 in anhydrous methylene chloride at $-30\text{ }^{\circ}\text{C}$ is added methanesulfonyl chloride (601 μL , 7.8 mmol), then triethylamine (1.5 mL, 11.1 mmol), and the reaction is stirred at $0\text{ }^{\circ}\text{C}$ 15 min. The resulting precipitate is filtered, and the filtrate is added to *N*-methyloamylamine (2.1 mL, 16.7 mmol). The reaction stirred at room temperature 16 h. The solution is concentrated under reduced pressure, redissolved in ethyl acetate and washed with saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (silica, 20% ethyl acetate/hexanes) provides the title compound. ESI MS m/z 264.2 $[M + H]^+$.

Step 2

- 5 N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{{[isopentyl(methyl)amino]methyl}}-5-methylbenzamide dihydrochloride

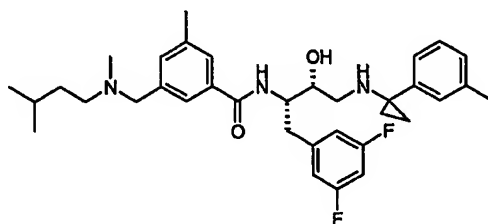


2 HCl

- 10 To methyl 3-{{[isopentyl(methyl)amino]methyl}}-5-methylbenzoate (250 mg, 0.95 mmol) in tetrahydrofuran/methanol/water (2:1:1, 8 mL) is added lithium hydroxide monohydrate (80 mg, 1.9 mmol), and the reaction is stirred at room temperature 16 h. The solution is
- 15 concentrated under reduced pressure, redissolved in DMF (5 mL), and diisopropylethylamine (660 μ L, 3.8 mmol), HATU (540 mg, 1.4 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{{[1-(3-ethynylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride (450 mg, 1.05 mmol) are added. The reaction
- 20 stirred at room temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene
- 25 chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 588.3 $[M + H]^+$.

EXAMPLE SP-212

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-3-
 5 { [isopentyl(methyl)amino]methyl }-5-methylbenzamide
 dihydrochloride



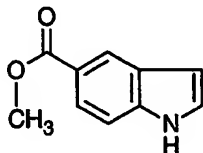
2 HCl

To methyl 3-([isopentyl(methyl)amino]methyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-211, Step
 10 1 (160 mg, 0.61 mmol) in tetrahydrofuran/methanol/water (2:1:1, 8 mL) is added lithium hydroxide monohydrate (51 mg, 1.2 mmol), and the reaction is stirred at room temperature 16 h. The solution is concentrated under reduced pressure, redissolved in DMF (5 mL), and diisopropylethylamine (424 μ L,
 15 2.4 mmol), HATU (290 mg, 0.8 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-([1-(3-ethylphenyl)cyclopropyl]amino)-3-methylbutan-2-ol dihydrochloride prepared by the method in
 EXAMPLE SP-272 (291 mg, 0.7 mmol) are added. The reaction stirred at room temperature 2 h. The reaction mixture is
 20 diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The
 25 residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 592.3 $[M + H]^+$.

EXAMPLE SP-213

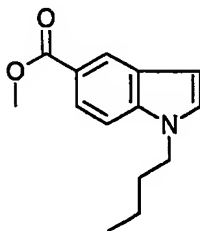
1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

5 Step 1: Methyl 1H-indole-5-carboxylate



To a mixture of indole-5-carboxylic acid (3.0 g) and triethylamine (1.9 g) in dry THF (100 mL) was added 1,1-carbonyldiimidazole (3.08 g). The mixture was stirred for 30
10 minutes at room temperature, at which time methanol (25 mL) was added. The mixture was stirred at room temperature for 1 h, partitioned between water and ethyl acetate. The layers were separated and the organic layer washed twice with water, dried over anhydrous magnesium sulfate, filtered and
15 concentrated under reduced pressure. Column chromatography on silica gel (200 mL) using CH₂Cl₂ as eluent to give 0.794 g of the title compound: ¹H NMR (CDCl₃) δ 3.93, 6.66, 7.28, 7.41, 7.91, 8.34, 8.42.

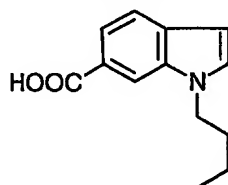
20 Step 2: Methyl 1-butyl-1H-indole-5-carboxylate



To a mixture of methyl 1H-indole-5-carboxylate (6.0 g) in methylsulfoxide (30 mL) was added potassium t-butoxide (3.88 g). The mixture was stirred at room temperature for 10
25 minutes at which time 1-iodobutane (1.8 mL) was added. The mixture was stirred at room temperature for 5 h then partitioned between water and methylene chloride. The layers

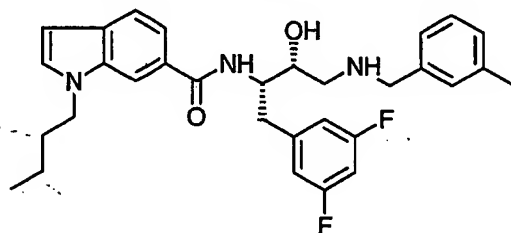
were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 10% ethyl acetate in hexanes as eluent to give
 5 6.18 g of the title compound: ^1H NMR (CDCl_3) δ 0.923, 1.38, 1.83, 3.9, 4.14, 6.58, 7.15, 7.34, 7.9, 8.39.

Step 3: 1-Butyl-1H-indole-6-carboxylic acid



10 To a mixture of 1-butyl-1H-indole-6-carboxylic acid (0.52 g) in methanol (25.0 mL) and water (5.0 mL) was added lithium hydroxide monohydrate (2.0 g). The mixture was heated to 60 °C for 6 h, cooled to room temperature, poured into 1N HCl (50mL) and extracted into ethyl acetate. The ethyl acetate extract
 15 was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.496 g (72%) of the title compound: ^1H NMR (CDCl_3) δ 0.98 (t, J = 7.3 Hz, 3 H), 1.4 (m, 2 H), 1.9 (m, 2 H), 4.2 (m, 2 H), 6.57 (ss, J = 2.6 Hz, 1 H), 7.31 (ss, J = 3.1 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.89
 20 (dd, J = 1.4, 8.4 Hz, 1 H), 8.24 (s, 1 H).

Step 4: 1-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-6-carboxamide



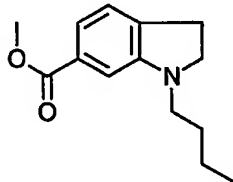
25 To a mixture of 1-butyl-1H-indole-6-carboxylic acid (0.278 g) in methylene chloride (10 mL) was added triethylamine (0.129 g), HOBT (0.175 g) and, HATU (0.486 g).

The mixture was stirred at room temperature for 30 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.408 g) was added. The resulting mixture was stirred at room temperature for 18 h then partitioned between water and methylene chloride. The layers were separated and the organic layer washed with water followed by brine and dried over anhydrous magnesium sulfate. Column chromatography on silica gel (100 mL) using 3% methanol in methylene chloride as eluent to give 0.256 g of the title compound: MS (ESI+) for $C_{32}H_{37}F_2N_3O_2$ m/z 542.2 (M+H).

EXAMPLE SP-201

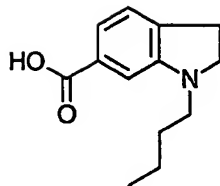
1-Butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]indoline-6-carboxamide hydrochloride

Step 1: Methyl 1-butylindoline-6-carboxylate



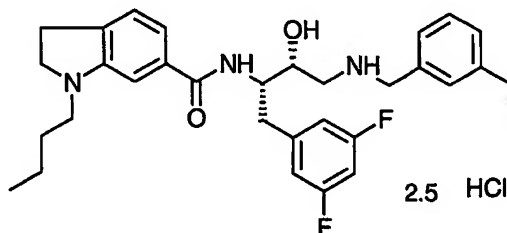
To a mixture of methyl 1-butyl-1H-indole-6-carboxylate, (2.1 g) in glacial acetic acid (25 mL) was added sodium cyanoborohydride (2.28 g). The mixture was heated at 40 °C for 3 h then cooled to room temperature, partitioned between water and ethyl acetate and the layers were separated. The organic layer was washed three times with brine, dried over anhydrous sodium sulfate and concentrated to give 1.64 g of the title compound: 1H NMR ($CDCl_3$) δ 0.969, 1.43, 1.59, 2.99, 3.1, 3.4, 3.88, 7.07, 7.34.

Step 2: 1-Butylindoline-6-carboxylic acid



To a mixture of Methyl 1-butylindoline-6-carboxylate (1.6 g) in methanol (20 mL) was added 1N NaOH (5.0 mL). The mixture was heated at 60 °C for 2 h then cooled to room temperature, poured into 1N HCl and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated to give 1.16 g of the title compound: ^1H NMR (CDCl_3) δ 0.974, 1.43, 1.60, 3.01, 3.11, 3.42, 7.1, 7.43.

Step 3: 1-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)indoline-6-carboxamide hydrochloride



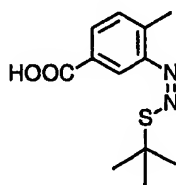
To a mixture of 1-butylindoline-6-carboxylic acid (0.2 g) in methylene chloride was added triethylamine (0.027 g), HOBT (0.125 g) and, HATU (0.347 g). The mixture was stirred at 40 °C for 15 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.346 g) was added. The resulting mixture was stirred at 40 °C for 5 h then partitioned between water and methylene chloride. The layers were separated and the organic layer washed with water followed by brine and dried over anhydrous magnesium sulfate. Column chromatography on silica gel (100 mL) using 5% methanol

in methylene chloride as eluent to give 0.100 g of the title compound: MS (ESI+) for $C_{32}H_{39}F_2N_3O_2$ m/z 535.9 (M+H)⁺.

EXAMPLE SP-215

- 5 1-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indazole-6-carboxamide

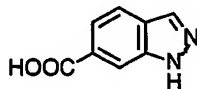
Step 1: 3-[(E)-(Tert-butylthio)diazenyl]-4-methylbenzoic acid



10

- To a mixture of 3-amino-4-methyl benzoic acid (5.0 g) in water (50 mL) was added concentrated hydrochloric acid (15 mL). The mixture was chilled to 0 °C in an ice/acetone bath.
- 15 Sodium nitrite (2.28 g) was dissolved in water (10 mL) and slowly added to the mixture at 0 °C. The pH was adjusted to 6 with saturated sodium acetate and 2-methyl-2-propanethiol (1.8 mL) was added. The mixture was stirred for 1 h and the resulting solids were collected by filtration, washed with
- 20 water and dried under reduced pressure to give 5.7 g of the title compound: ¹H NMR (CDCl₃) δ 1.61, 2.20, 7.38, 7.55, 9.67.

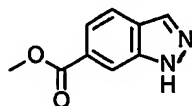
Step 2: 1H-Indazole-6-carboxylic acid



- 25 To a mixture of 3-[(E)-(tert-butylthio)diazenyl]-4-methylbenzoic acid (5.7 g) in nitrogen degassed methylsulfoxide (90 mL) was added potassium t-butoxide (25.0 g). The mixture was stirred at room temperature for 24 h then poured onto ice and acidified to pH 4 with concentrated
- 30 hydrochloric acid. The mixture was extracted with diethyl

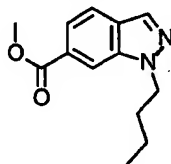
ether and the organic layer washed with brine. The organic layer was dried over anhydrous magnesium sulfate and decolorizing carbon then concentrated under reduced pressure to give 1.2 g of the title compound: ^1H NMR (CDCl_3) δ 0.963, 1.36, 1.95, 4.48, 7.81, 7.88, 8.08, 8.29.

Step 3: Methyl 1H-indazole-6-carboxylate



To a mixture of 1H-indazole-6-carboxylic acid (1.0 g) in methylene chloride (15 mL) was added EDC (1.8 g), HOBT (1.27 g), and triethylamine (1.29 mL). The mixture was heated to 40 °C for 30 minutes at which time methanol (10.0 mL) was added. The mixture was stirred at 40 °C for 18 h. The mixture was removed from heat, cooled to room temperature and poured into methylene chloride. The mixture was washed twice with water then brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 0.955 g of the title compound: ^1H NMR (CDCl_3) δ 3.98, 7.81, 7.86, 8.16, 8.29, 10.6.

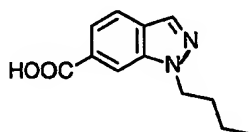
Step 4: Methyl 1-butyl-1H-indazole-6-carboxylate



To a mixture of methyl 1H-indazole-6-carboxylate (0.95 g) in DMF (10 mL) was added 60% NaH (0.216 g). The mixture was heated to 60 °C and 1-iodobutane (0.61 mL) was added. The mixture was heated at 60 °C for 72 h and 1-iodobutane (0.61 mL) was added every 24 h. The mixture was removed from heat and cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic

layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% ethyl acetate in hexanes as eluent to give 0.356 g of the title compound: ^1H NMR (CDCl_3) δ 0.938, 1.34, 1.92, 3.97, 4.43, 7.73, 7.79, 8.03, 8.18.

Step 5: 1-Butyl-1H-indazole-6-carboxylic acid

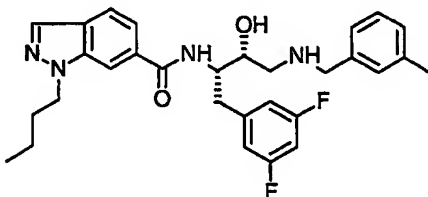


10

To a mixture of methyl 1-butyl-1H-indazole-6-carboxylate (0.356 g) in methanol (10 mL) was added saturated sodium bicarbonate (5 mL). The mixture was heated at 60 °C for 2 h at which time 1N NaOH (5 mL) was added and the mixture heated to 80°C for 18 h. The mixture was cooled to room temperature, poured into 1N HCl (50 mL), and extracted with ethyl acetate. The ethyl acetate extract dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.310 g of the title compound: ^1H NMR (CDCl_3) δ 0.964, 1.96, 4.48, 7.81, 7.89, 8.29, 8.46.

20

Step 6: 1-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indazole-6-carboxamide



25

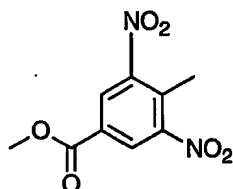
To a mixture of 1-butyl-1H-indazole-6-carboxylic acid (0.2 g) in methylene chloride (20 mL) was added triethylamine (0.182 g), HOBT (126 g), and HATU (0.348 g). The mixture was

stirred at 40 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.35 g) was added. The mixture was stirred at 40 °C for 3 h then poured into methylene chloride (50 mL), washed with water then brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent to give 0.2 g of the title compound: MS (ESI+) for $C_{31}H_{36}F_2N_4O_2$ m/z 534.9 (M+H)⁺.

EXAMPLE SP-216

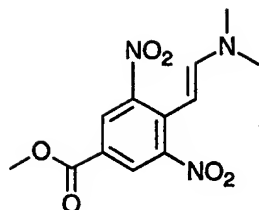
1-Butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide

Step 1: Methyl 4-methyl-3,5-dinitrobenzoate



To a mixture of 3,5 dinitrotoluic acid (16 g) in methanol (10 mL) was added sulfuric acid (15 mL). The mixture was heated to 75 °C for 72 h, removed from heat and cooled to room temperature. The solvents were removed under pressure and the residue was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed with 2 N NaOH followed by water. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give 16.28 g (96%) of the title compound: ¹H NMR (CDCl₃) δ 2.65 (s, 3 H), 4.02 (s, 3 H), 8.61 (s, 2 H

Step 2: Methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate

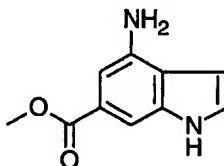


To a mixture of methyl 4-methyl-3,5-dinitrobenzoate (5.6 g) in toluene (20 mL) was added dimethylformamide dimethyl acetal (4.17 g) and 5-sulfo salicylic acid hydrate (0.1 g).

5 The mixture was heated to 110 °C for 19 h, removed from heat and cooled to room temperature. The solvents were removed under reduced pressure at which time hexanes was added to the residue and the residue was filtered to give 6.85 g of the title compound: ^1H NMR (CDCl_3) δ 2.97, 3.96, 5.54, 6.74, 8.33.

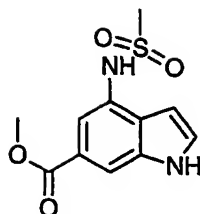
10

Step3: Methyl 4-amino-1H-indole-6-carboxylate



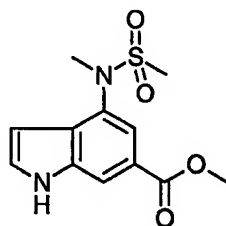
To a mixture of methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (19.3 g) in ethyl acetate (200 mL) was added 5% palladium on carbon (1.5 g). The mixture was placed under 45 PSI H_2 and shaken overnight. The mixture was filtered through celite and concentrated. The residue was dissolved in CH_2Cl_2 to which was added ((1:1) H_2O :conc. HCl (250 mL)). The resulting solids were collected by filtration, dissolved in ethyl acetate and washed with 2N NaOH . The ethyl acetate layer with anhydrous magnesium sulfate, filtered and concentrated to give 7.4 g of the title compound: ^1H NMR (CDCl_3) δ 3.91, 4.01, 6.51, 7.09, 7.27, 8.40.

25 Step 4: Methyl 4-[(methylsulfonyl)amino]-1H-indole-6-carboxylate



To a mixture of methyl 4-amino-1H-indole-6-carboxylate (1.0 g) in DMF (10 mL) was added 4-dimethylaminopyridine (1.46 g) and methanesulfonyl chloride (0.6 g). The mixture was
 5 heated to 60 °C for 3 h, cooled to room temperature, and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous sodium sulfate and concentrated to give 0.71 g of the title compound: ¹H NMR (CDCl₃) δ 3.02, 3.94,
 10 6.69, 7.42, 7.81, 8.04.

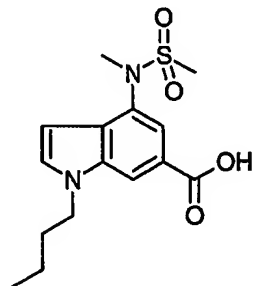
Step 5: Methyl 4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylate



15 To a mixture of Methyl 4-[(methylsulfonyl)amino]-1H-indole-6-carboxylate (0.6 g) in THF (10 mL) was added potassium carbonate (0.309 g) and iodomethane (0.63 mL). The mixture was stirred at room temperature for 4 h then heated to 40 °C overnight. Iodomethane (0.3 mL) was added and the
 20 mixture heated an additional 3 h. The mixture was cooled to room temperature, partitioned between water and diethyl ether, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in ether and decolorizing carbon (2 g) was added and the mixture refluxed for 5 minutes then filtered
 25 through celite while hot. The ether was removed under reduced

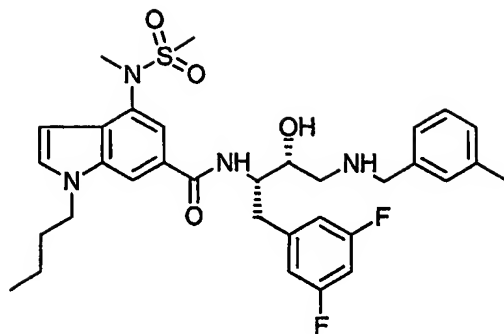
pressure to give 0.437 g of the title compound: MS (ESI+) for C₁₂ H₁₄ N₂ O₄ S₁ m/z 321.1 (M+K).

Step 6: 1-Butyl-4-[methyl(methylsulfonyl)amino]-1H-indole-6-
5 carboxylic acid



To a mixture of methyl 4-[methyl(methylsulfonyl)amino]-
1H-indole-6-carboxylate (0.437 g) in DMF(15 mL) was added
potassium hydroxide (0.087 g) and iodobutane (0.34 mL). The
10 mixture was heated to 70 °C for 6 h. then stirred at room
temperature for 72 h. The mixture was partitioned between
water and ethyl acetate, the layers were separated and the
organic layer washed three times with water. The organic
layer was dried over anhydrous sodium sulfate, filtered and
15 concentrated. The residue was dissolved in methanol (5 mL) to
which was added 1N NaOH (2 mL) and the mixture heated to 50 °C
for 1 h. The mixture was cooled to room temperature and
poured into water and washed with ether. The aqueous layer
was acidified to pH 4 with 1N HCl and the product extracted
20 into ethyl acetate which was dried over anhydrous sodium
sulfate, filtered and concentrated to dryness to give 0.377 g
of the title compound: ¹H NMR (CDCl₃) δ 0.973, 1.38, 1.87,
3.01, 3.45, 4.21, 6.71, 7.36, 7.82, 8.18.

25 Step 7: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
ethylbenzyl)amino]-2-hydroxypropyl}-4-
[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide

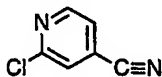


To a mixture of 1-Butyl-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylic acid (0.2g) in methylene chloride (15 mL) was added triethylamine (0.156 g), HOBT (0.105 g), and HATU (0.293 g). The mixture was stirred at 39 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.293 g) was added. The mixture was stirred at 40 °C for 4 h then poured into methylene chloride (50 mL), washed with water followed by brine then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent to give 0.21 g of the title compound: MS (ESI+) for $C_{34}H_{42}F_2N_4O_4S_1$ m/z 640.8 (M+H).

EXAMPLE SP-217

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide hydrochloride

Step 1: 2-Chloroisonicotinonitrile

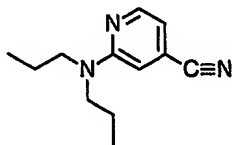


4-cyanopyridine-N-oxide (10.0 g) was added to phosphorus oxychloride (85 mL) and heated to 110 °C for 2.5 h. The mixture was cooled to room temperature and the excess phosphorus oxychloride removed under reduced pressure. The residue was dissolved in water and made basic with concentrated ammonia. The product was extracted into

methylene chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using methylene chloride as eluent to give 7.19 g of the title compound: ^1H NMR (CDCl_3) δ 7.48, 7.6, 8.6.

5

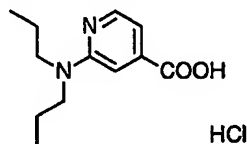
Step 2: 2-(Dipropylamino)isonicotinonitrile



2-Chloroisonicotinonitrile (1.0 g) and dipropylamine (10 mL) were placed in a sealed heavy wall tube and heated to 100
10 °C for 18 h. The mixture was removed from heat and cooled to room temperature. The dipropylamine was removed under reduced pressure and the residue chromatographed on silica gel using 2% ethyl acetate in hexanes as eluent to give 1.06 g of the title compound: MS (ESI+) for $\text{C}_{12}\text{H}_{17}\text{N}_3$ m/z 204.1 ($\text{M}+\text{H}$) $^+$.

15

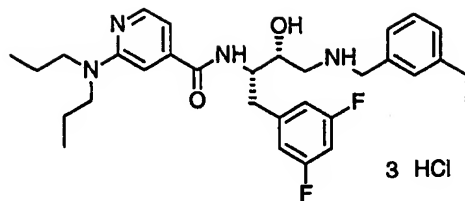
Step 3: 2-(Dipropylamino)isonicotinic acid hydrochloride



2-(Dipropylamino)isonicotinonitrile (1.0 g) was dissolved in concentrated hydrochloric acid (30 mL) and heated at 65 °C
20 for 3 h. The solvents were removed under reduced pressure to give 1.27 g of the title compound: MS (ESI+) for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2$ m/z 237.3 ($\text{M}+\text{H}$) $^+$.

Step 4: N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide hydrochloride

25



To a mixture of 2-(Dipropylamino)isonicotinic acid hydrochloride (0.2g) in methylene chloride (15 mL) was added triethylamine (0.195 g), HOBT (0.105 g), and HATU (0.293 g).
 5 The mixture was stirred at 39 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.285 g) was added. The mixture was stirred at 40 °C for 4 h then poured into methylene chloride (50 mL), washed with water then brine, dried over
 10 anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent and conversion to the hydrochloride salt gave 0.105 g of the title compound: MS (ESI+) for $C_{31}H_{40}F_2N_4O_2$ m/z 539.3 (M+H)⁺.

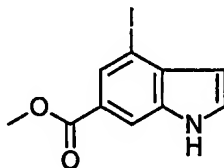
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EXAMPLE SP-218

1-Butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide

20

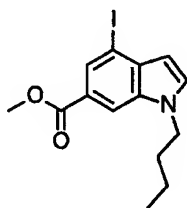
Step 1: Methyl 4-iodo-1H-indole-6-carboxylate



To a mixture of methyl 4-amino-1H-indole-6-carboxylate (EXAMPLE SP-216, step 3) (3.2 g) in water (50 mL) was added
 25 concentrated hydrochloric acid (5 mL). The mixture was chilled to below 5 °C with the addition of ice. To this was added sodium nitrite (1.16 g) dissolved in water (10 mL). The

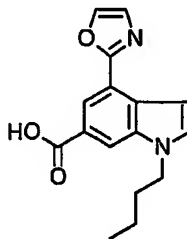
mixture was stirred chilled for 1 h followed by addition of sodium iodide (3 g) in water (20 mL). The mixture was stirred for 30 minutes, filtered and the solids collected by filtration were washed with water and dried at 50 °C. The solids turned black and gas evolved rapidly upon drying. Column chromatography on silica gel (200 mL) using 20 % hexanes in CH₂Cl₂ as eluent to give 0.82 g of the title compound: ¹H NMR (CDCl₃) δ 3.94, 6.55, 7.43, 8.14, 8.22, 8.62.

10 Step 2: Methyl 1-butyl-4-iodo-1H-indole-6-carboxylate



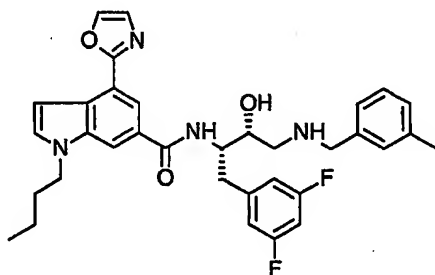
To a mixture of methyl 4-iodo-1H-indole-6-carboxylate (1.0 g) in DMF (10 mL) was added potassium hydroxide (0.392 g) and 1-iodobutane (0.8 mL). The mixture was heated to 80 °C for 18 h. The mixture was cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed twice with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 20% ethyl acetate in hexanes as eluent to give 0.73 g of the title compound: ¹H NMR (CDCl₃) δ 0.940, 1.32, 1.81, 3.95, 4.15, 6.45, 7.31, 8.09, 8.18.

25 Step 3: 1-Butyl-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxylic acid



To a -72 °C solution of oxazole (0.069 g) in dry THF (20 mL) was added dropwise 1.6 M N-butyl lithium (0.68 mL). The mixture was stirred at -72 °C for 30 minutes at which time 1.0 M zinc chloride (3.3 mL) was added. The mixture was allowed to warm to 0 °C at which time methyl 1-butyl-4-iodo-1H-indole-6-carboxylate (0.37 g) and tetrakis triphenylphosphine palladium (0) (0.07 g) were added and the mixture heated to 85 °C. The mixture was heated at 85 °C for 20 h then cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography was performed on silica gel (100 mL) using 20% ethyl acetate in hexanes as eluent. The residue was dissolved in methanol (10 mL) and 1N NaOH (3 mL) and heated at 60 °C for 2 h. The mixture was acidified to pH 4 with 1N HCl and extracted with ethyl acetate. The ethyl acetate extracts were dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.2 g of the title compound: MS (ESI+) for C₁₆H₁₆N₂O₃ m/z 283.16 (M+H)⁺.

Step 4: 1-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide



To a mixture of 1-butyl-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxylic acid (0.2g) in methylene chloride (20 mL) was added 1,1-carbonyldiimidazole (0.114 g). The mixture was stirred at room temperature for 1 h at which time (2R,3S)-3-amino-4-(3,5-

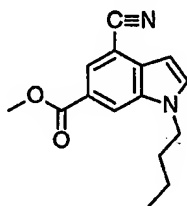
difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.265 g) dissolved in methylene chloride (10 mL) was added. The mixture was stirred at room temperature for 18 h then poured into methylene chloride (50 mL), washed with water followed by
5 brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 65% methylene chloride, 30 % hexanes, and 5% methanol as eluent to give 0.0985 g of the title compound: MS (ESI+) for $C_{35}H_{38}F_2N_4O_3$ m/z 601.99 (M+H)⁺.

10

EXAMPLE SP-219

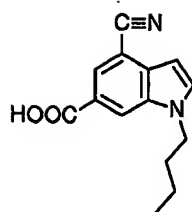
1-Butyl-4-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

15 Step 1: Methyl 1-butyl-4-cyano-1H-indole-6-carboxylate



To a mixture of methyl 1-butyl-4-iodo-1H-indole-6-carboxylate (EXAMPLE SP-218, Step 4) (1.47 g) in N-methyl pyrrolidinone (15 mL) was added copper (I) cyanide (1.1 g).
20 The mixture was heated to 150 °C for 6 h, removed from heat and cooled to room temperature. The mixture was partitioned between water and ethyl acetate and the layers were separated. The organic layer was washed three times with water, dried over anhydrous sodium sulfate and concentrated under reduced
25 pressure. Column chromatography on silica gel (100 mL) using 20% ethyl acetate as eluent to give 0.5 g of the title compound: ¹H NMR (CDCl₃) δ 0.955, 1.32, 1.85, 3.98, 4.23, 6.76, 7.43, 8.16, 8.30.

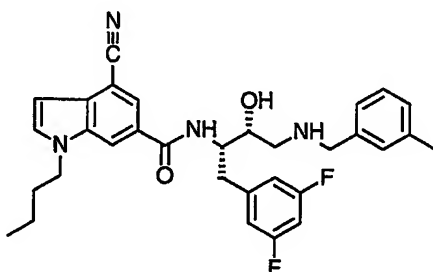
30 Step 2: 1-Butyl-4-cyano-1H-indole-6-carboxylic acid



To a mixture of methyl 1-butyl-4-cyano-1H-indole-6-carboxylate (10.5 g) in methanol (15 mL) was added 1N NaOH (3.0 mL). The mixture was heated at 40 °C for 2 h then cooled
 5 to room temperature. The mixture was poured into 1N HCl and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated to give 0.45 g of the title compound: ¹H NMR (CDCl₃) δ 0.973, 1.38, 1.88, 4.27, 6.79, 7.48, 8.24, 8.38.

10

Step 3: 1-Butyl-4-cyano-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1H-indole-6-carboxamide



15 To a mixture of 1-butyl-4-cyano-1H-indole-6-carboxylic acid (0.29 g) in methylene chloride (10 mL) was added 1,1-carbonyldiimidazole (0.194 g) and triethylamine (0.267 g). The mixture was stirred at room temperature for 45 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.5 g) dissolved in methylene
 20 chloride (10 mL) was added. The mixture was stirred at room temperature for 18 h then poured into methylene chloride (50 mL), washed with water followed by brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column
 25 chromatography on silica gel (100 mL) using 5% methanol in

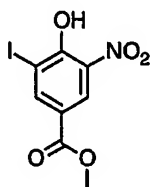
methylene chloride as eluent to give 0.47 g of the title compound: MS (ESI+) for $C_{33}H_{36}F_2N_4O_2$ m/z 559.0 (M+H)⁺.

EXAMPLE SP-220

- 5 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

Step 1: Methyl 4-hydroxy-3-iodo-5-nitrobenzoate

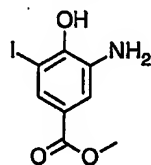
10



- To a solution of methyl 4-hydroxy-3-nitrobenzoate (2.0 g) in acetic acid (15 mL) was added iodine monochloride (1.65 mg) in acetic acid, and the mixture was stirred at 100 °C for 1.5 h. After cooling to room temperature, the mixture was poured into water (200mL), and stirred for 30 min. The mixture was filtered and washed with water and hexanes. The yellow powder was collected by filtration and dried in vacuum oven overnight to give 2.99 g of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 11.68, 8.81, 8.72, 3.96.

20

Step 2: Methyl 3-amino-4-hydroxy-5-iodobenzoate

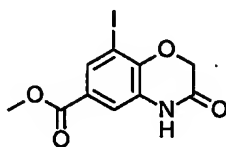


- To a mixture of methyl 4-hydroxy-3-iodo-5-nitrobenzoate (2.99 g) in ethanol (40 mL) was added tin (II) chloride (10 g) portion wise. After stirring for 1 h at reflux, the mixture was cooled to 0 °C and quenched by saturated potassium carbonate (100 mL). The mixture was filtered through

25

diatomaceous earth and the filtrate was extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 2.5 g of the title compound: ^1H NMR (300 MHz, DMSO- d_6) δ 7.50, 7.24, 3.75.

Step 3: Methyl 8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

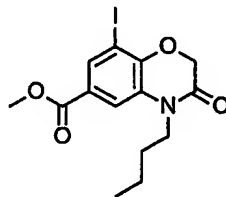


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To an ice-cold, stirred solution of Methyl 3-amino-4-hydroxy-5-iodobenzoate (2.3 g) and sodium bicarbonate (1.5 g) in 1:1 isobutyl methyl ketone/water (80 mL) was added chloroacetyl chloride (1.1 g), and the reaction mixture was stirred for 1 h. The mixture was warmed to room temperature and heated at reflux for 18 h. After overnight, a beige solid formed. The mixture was filtered, and washed with water and hexanes to give 2.4 g of the title compound: ^1H NMR (300 MHz, DMSO- d_6) δ 10.98, 7.89, 7.47, 4.79, 3.82.

20

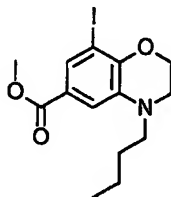
Step 4: Methyl 4-butyl-8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To a solution of Methyl 8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (2.64 g) and potassium carbonate (5 g) in DMSO (20 mL) was added bromobutane (5 g), and the reaction mixture was stirred for 1 h at 80 °C. The mixture was cooled to room temperature, diluted with 1:1 ethyl

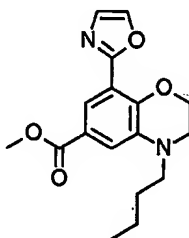
acetate/hexanes (100 mL) and water (160 mL), and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:10 ethyl acetate/hexanes) afforded 2.24 g of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 8.13, 7.63, 4.74, 3.96, 3.92, 1.64, 1.42, 0.97.

Step 5: Methyl 4-butyl-8-iodo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



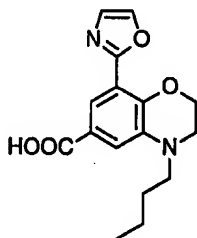
A solution of Methyl 4-butyl-8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (680 mg) and 9-BBN (900 mg) in tetrahydrofuran (30 mL) was heated at reflux for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.22 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% ethyl acetate/hexanes) afforded 600 mg of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 7.75, 7.28, 4.34, 3.86, 3.36, 3.28, 1.58, 1.40, 0.96.

Step 6: Methyl 4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To a -70°C solution of oxazole (227 mg) in tetrahydrofuran (10 mL) was added *n*-butyllithium (2.5 M in hexanes, 2 mL). After stirred at -70°C for 30 min, zinc chloride (1 M in ethyl ether, 13 mL) was added: The mixture
5 was warmed to 0°C for 1 h. To this mixture was then added ethyl 4-butyl-8-iodo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (600 mg, 1.6 mmol) in THF (5 mL) followed by tetrakis triphenylphosphine palladium (0) (115 mg). The mixture was heated at reflux for 3 h, diluted with ethyl
10 acetate (300 mL) and washed with water followed by brine. The organic solution was dried (sodium sulfate) and concentrated under reduced pressure. Purification by silica gel plug (1:1 acetate/hexanes) provided 363 mg of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 7.96, 7.73, 7.40, 7.28, 4.44, 3.90, 3.43,
15 3.34, 1.61, 1.41, 0.98.

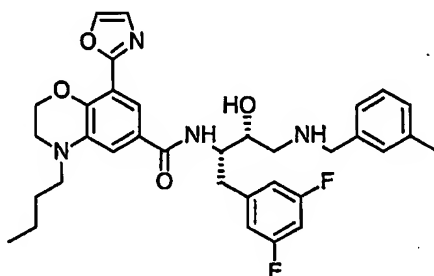
Step 7: 4-Butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid



To a stirred solution of Methyl 4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (474 mg) in methanol (20 mL) was added potassium hydroxide (15 mL of a 1.0 M solution in water). The mixture was stirred at room temperature overnight then concentrated under reduced
25 pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to
30 give 450 mg of the title compound: ^1H NMR (300 MHz, CDCl_3)

8.11.60, 8.08, 7.74, 7.46, 7.37, 4.46, 3.43, 3.34, 1.62, 1.41, 0.98.

Step 8: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

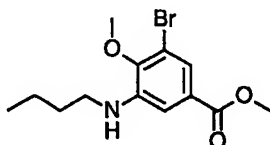


A solution of 4-Butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (450 mg, HBTU (853 mg), and diisopropylethylamine (580 mg) was stirred in methylene chloride (15 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (606 mg) in methylene chloride (7 mL) was added and the reaction mixture was stirred overnight. The mixture was filtered with methylene chloride, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 400 mg of the title compound: ESI MS m/z 619 $[M + H]^+$.

EXAMPLE SP-221

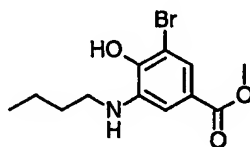
4-Butyl-8-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

Step 1: Methyl 3-bromo-5-(butylamino)-4-methoxybenzoate



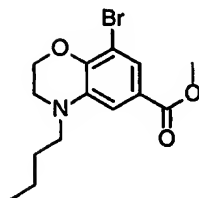
To a stirred solution of Pd(OAc)₂ (144 mg), BINAP (1.2 g), and cesium carbonate (8.4 g) in toluene (100 mL) was added butylamine (1.6 mL), and the mixture was heated at 80 °C for 15 min. A solution methyl 3,5-dibromo-4-methoxybenzoate (4.2 g) in toluene (30 mL) was added dropwise over 20 min. The mixture was refluxed overnight. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided 3.5 g of the title compound: ¹H NMR (300 MHz, CDCl₃) δ.7.52, 7.19, 3.90, 3.88, 3.18, 1.66, 1.46, 0.97.

Step 2: Methyl 3-bromo-5-(butylamino)-4-hydroxybenzoate



To a -78 °C solution of the Methyl 3-bromo-5-(butylamino)-4-methoxybenzoate (520 mg) in methylene chloride (10 mL) was added BBr₃ (8 ml of 1.0 M solution in methylene chloride) dropwise and the reaction mixture was stirred for 18 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride and saturated sodium bicarbonate was added. The mixture was cooled to 0 °C and methanol was added dropwise. After stirring for 30 min, the mixture was stirred at room temperature for 1 h. The solvent was removed, and the residue dissolved in methylene chloride, washed with water, saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:20, ethyl acetate/hexanes) provided 440 mg of the title compound: ¹H NMR (300 MHz, CDCl₃) δ.7.52, 7.19, 3.88, 3.18, 1.65, 1.46, 0.97.

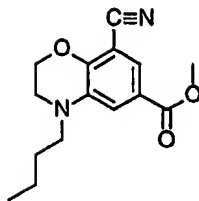
Step 3: Methyl 8-bromo-4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To an ice-cold, stirred solution of Methyl 3-bromo-5-
5 (butylamino)-4-hydroxybenzoate (440 mg) and sodium bicarbonate
(280 mg) in 1:1 isobutyl methyl ketone/water (10 mL) was added
chloroacetyl chloride (226 mg). The mixture was stirred for 1
h, warmed to room temperature, and heated at reflux for 14 h.
The mixture was cooled to room temperature, diluted with
10 chloroform, and the layer separated. The organic layer was
washed with water, and brine, dried (magnesium sulfate),
filtered, and concentrated under reduced pressure to give a
white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.94, 7.62, 4.76, 3.98,
3.93, 1.65, 1.43, 0.97, which was used in the next step
15 without further purification or characterization.

Step 4: A solution of the amide from step 3 and 9-BBN
(780 mg) in tetrahydrofuran (10 mL) was heated at reflux for
1.5 h. The mixture was cooled to room temperature,
ethanolamine (0.2 mL) was added, and the resulting solution
20 was concentrated under reduced pressure. The residue was
washed with hexanes, filtered, and the filtrate was
concentrated under reduced pressure. Purification by flash
column chromatography (silica, 10% ethyl acetate/hexanes)
afforded (330 mg, over 2 steps) of the title compound: ^1H NMR
25 (300 MHz, CDCl_3) δ 7.55, 7.27, 4.36, 3.87, 3.37, 3.30, 1.60,
1.41, 0.97.

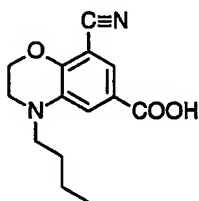
Step 5: Methyl 4-butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To a flask containing methyl 8-bromo-4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (0.33 g) was added NMP (7 mL), followed by copper cyanide (0.18 g). The mixture was then heated to 175 °C and stirred overnight. The resulting mixture was cooled to room temperature and poured into 1 N hydrochloric acid. The acidic aqueous layer was extracted with ethyl acetate, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided 184 mg of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 7.55, 7.43, 4.41, 3.89, 3.39, 3.31, 1.58, 1.40, 0.97.

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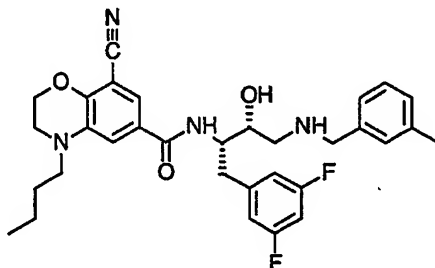
Step 6: 4-Butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid



To a stirred solution of Methyl 4-butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (184 mg) in methanol (3 mL) was added potassium hydroxide (7 mL of a 1.0 M solution in water). The mixture was stirred at room temperature overnight then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and

concentrated under reduced pressure to give 154 mg of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 7.62, 7.46, 4.44, 3.41, 3.33, 1.60, 1.41, 0.98.

- 5 Step 7: 4-Butyl-8-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

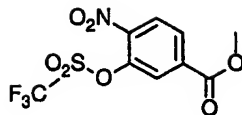


- A solution of 4-Butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (129 mg), HBTU (284 mg), and diisopropylethylamine (0.26 mL) was stirred in methylene chloride (6 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (204 mg) in methylene chloride (4 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 20 mg of the title compound: ESI MS m/z 577 $[\text{M} + \text{H}]^+$.

EXAMPLE SP-222

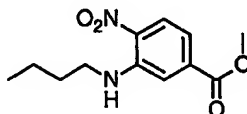
- 4-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

Step 1: Methyl 4-nitro-3-[[trifluoromethyl)sulfonyl]oxy]benzoate



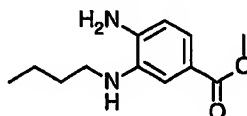
To an ice-cold, stirred solution of methyl 3-hydroxy-4-nitrobenzoate (1.5 g) and triethylamine (1.1 mL) in methylene chloride (15 mL) was added trifluoromethane sulfonic anhydride (1.4 mL), and the reaction mixture was stirred for 30 min. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure provided 2.4 g of the title compound: ^1H NMR (300 MHz, DMSO- d_6) δ 8.47, 8.27, 8.15, 3.99.

Step 2: Methyl 3-(butylamino)-4-nitrobenzoate



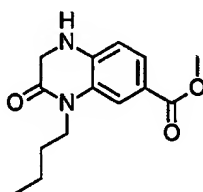
To a stirred solution of $\text{Pd}_2(\text{dba})_3$ (139 mg), BINAP (284 mg), and cesium carbonate (2.0 g) in toluene (50 mL) was added butylamine (0.45 mL), and the reaction mixture was heated at 80 °C for 15 min. A solution of methyl 4-nitro-3-([(trifluoromethyl)sulfonyl]oxy)benzoate (1.0 g) in toluene (15 mL) was added dropwise over 1 h. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 3:1 ethyl acetate/hexanes) provided 670 mg of the title compound as a yellow oil: ESI MS m/z 550 $[\text{M} + \text{H}]^+$.

Step 3: Methyl 4-amino-3-(butylamino)benzoate



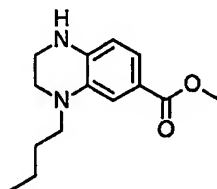
A solution of methyl 3-(butylamino)-4-nitrobenzoate (1.1 g) and 10% Pd/C (110 mg) in methanol (20 mL) was shaken under an atmosphere of hydrogen at 50 psi for 2 h. The mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide 940 mg of the title compound: ¹H NMR (300 MHz, DMSO-d₆) δ 7.13, 6.94, 6.52, 3.72, 3.02, 1.60, 1.42, 0.93.

Step 4: Methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



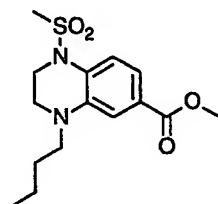
To an ice-cold, stirred solution of methyl 4-amino-3-(butylamino)benzoate (950 mg) and sodium bicarbonate (862 mg) in 1:1 isobutyl methyl ketone/water (20 mL) was added chloroacetyl chloride (0.41 mL), and the mixture was stirred for 1 h. The mixture was warmed to room temperature and refluxed for 14 h. The mixture was cooled to room temperature, diluted with chloroform, and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) afforded 850 mg of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 7.89, 7.72, 6.80, 3.97, 3.88, 3.30-3.25, 1.68-1.58, 1.47-1.35, 0.94-0.88.

Step 5: Methyl 4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



To an ice-cold, stirred solution of methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (840 mg) in tetrahydrofuran (32 mL) was added borane dimethylsulfide complex (3.2 mL, 2.0 M tetrahydrofuran) and the resulting mixture was refluxed for 24 h. The mixture was cooled to room temperature, quenched with methanol, and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided 364 mg of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 7.27, 7.22, 6.41, 3.84, 3.47-3.45, 3.32-3.23, 1.60-1.58, 1.42-1.37, 0.99-0.94.

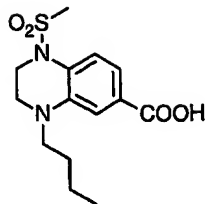
Step 6: Methyl 4-butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



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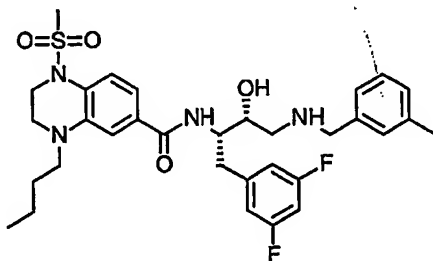
To an ice-cold, stirred solution of methyl 4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (180 mg) and triethylamine (62 μL) in methylene chloride (2 mL) was added methanesulfonyl chloride (101 μL) and the mixture was stirred for 1 h. The mixture was warmed to room temperature, diluted with methylene chloride, washed with washed with 1 N hydrochloric acid, and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:3 ethyl acetate/hexanes) provided 150 mg of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 7.57, 7.41, 7.32, 3.90, 3.84, 3.45, 3.38, 1.61, 1.41, 0.98.

Step 7: 4-Butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid



To a stirred solution of methyl 4-butyl-1-(methanesulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (144 mg) in methanol (1.3 mL) was added 1 M potassium hydroxide (13 mL). The mixture was stirred at room temperature for 48 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 99 mg of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 7.43, 7.39, 7.24, 3.77, 3.39, 3.32, 1.56, 1.33, 0.90.

Step 8: 4-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methanesulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide



A solution of 4-butyl-1-(methanesulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (99 mg), HATU (181 mg), HOBT (64 mg), and diisopropylethylamine (100 μL) was stirred in methylene chloride (1.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (129 mg) and diisopropylethylamine (100 μL) in methylene chloride (1.0 mL) was added and the mixture was stirred overnight. The mixture

was diluted with methylene chloride, washed with 1 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure.

5 Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.5 mL, 1.0 M diethyl ether). The resulting precipitate was collected by filtration to provide 90 mg of the title

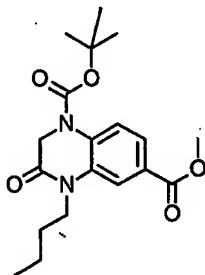
10 compound: ESI MS m/z 629 $[M + H]^+$.

EXAMPLE SP-223

4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-

15 tetrahydroquinoxaline-6-carboxamide hydrochloride

Step 1: 1-Tert-butyl 6-methyl 4-butyl-3-oxo-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate

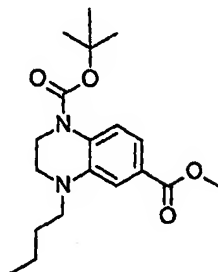


20 To an ice-cold, stirred solution of methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (1.1 g), and triethylamine (0.9 mL) in methylene chloride (10 mL) was added DMAP (51.3 mg) and di-tert-butyl dicarbonate (1.4 g), and the resulting mixture was stirred for 4 d. The mixture was

25 diluted with methylene chloride, washed with water, and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl

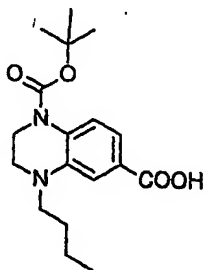
acetate/hexanes) provided 440 mg of the title compound: ESI MS m/z 363 $[M + H]^+$.

Step 2: 1-Tert-butyl 6-methyl 4-butyl-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate



A solution of 1-tert-butyl 6-methyl 4-butyl-3-oxo-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate (440 mg) and 9-BBN dimer (600 mg) in tetrahydrofuran (10 mL) was heated at 65 °C for 10 h. The mixture was cooled to room temperature, ethanolamine (0.15 mL) was added and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) afforded 158 mg of the title compound: 1H NMR (300 MHz, $CDCl_3$) δ 7.50, 7.34, 7.28, 3.88, 3.77, 3.38-3.30, 1.65-1.51, 1.42-1.34, 0.99-0.94.

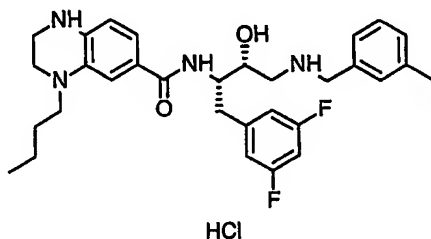
Step 3: 1-(Tert-butoxycarbonyl)-4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid



To a stirred solution of 1-tert-butyl 6-methyl 4-butyl-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate (158 mg) in

methanol (1.4 mL) was added 1 M potassium hydroxide (1.4 mL). The mixture was stirred at 40 °C for 12 h and then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was
 5 acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 120 mg of the title compound: ¹H NMR (300 MHz, CDCl₃) δ, 7.55, 7.40, 7.37, 3.79, 3.38, 3.34, 1.60,
 10 1.53, 1.39, 0.97.

Step 4: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoxaline-6-carboxamide hydrochloride



15

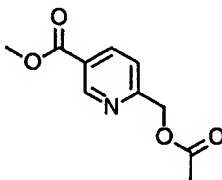
A solution of 1-(tert-butoxycarbonyl)-4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (120 mg), HBTU (204 g), and diisopropylethylamine (100 mL) was stirred in methylene chloride (2.0 mL) for 15 min. A solution of
 20 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (146 mg) and diisopropylethylamine (100 mL) in methylene chloride (2.0 mL) was added and the mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N
 25 hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was
 30 dissolved in methanol (1 mL), and treated with hydrochloric

acid (0.5 mL, 1.0 M diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide 45 mg of the title compound: ESI MS m/z 551 $[M + H]^+$.

5 EXAMPLE SP-224

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(methylsulfonyl)methyl]nicotinamide

Step 1: Methyl 6-[(acetyloxy)methyl]nicotinate

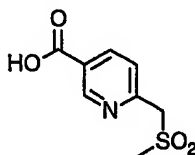


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To a solution of methyl 6-methylnicotinate (6.05 g) in methylene chloride (100 mL) was added *m*-chloroperbenzoic acid (77%, 13.5 g). The reaction mixture was stirred at room temperature for 2 h and then diluted with chloroform (100 mL).

15 The mixture was washed successively with aqueous sodium sulfite, saturated sodium bicarbonate, and brine. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 6.21 g of methyl 6-methylnicotinate 1-oxide. A solution of methyl 6-methylnicotinate 1-oxide (4.35 g) in acetic anhydride (50 mL)
20 was heated at 120 °C for 2 h and then concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1:2 to 3:5 ethyl acetate/hexanes) provided 3.3 g of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 9.18, 8.31,
25 7.44, 5.29, 3.96, 2.19.

Step 3: 6-[(Methylsulfonyl)methyl]nicotinic acid



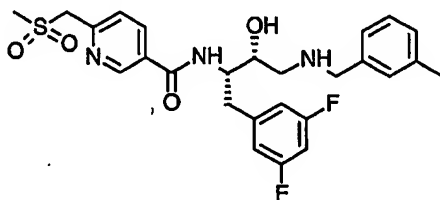
To a solution of methyl 6-[(acetyloxy)methyl]nicotinate (3.0 g) in dry methanol (100 mL) was added potassium carbonate (4.56 g). The mixture was stirred at room temperature for 2 h and then diluted with methylene chloride (200 mL) and water (200 mL). The organic layer was washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 1.70 g of the alcohol. This material was used without further purification. To an ice-cold solution of methyl 6-(hydroxymethyl)nicotinate (1.6 g) in methylene chloride (40 mL) was added diisopropylethylamine (1.5 g) followed by methanesulfonyl chloride (1.21 g). The mixture was stirred at room temperature for 1 h and then diluted with methylene chloride (100 mL). The mixture was washed successively with 0.5 N potassium hydrogen sulfate, water, and brine. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide mesylate 2.34 g. This mesylate was used without further purification.

To a solution of methyl 6-[[[(methylsulfonyl)oxy]methyl]nicotinate (2.34 g) in *N,N*-dimethylformamide (10 mL) was added sodium thiomethoxide (850 mg). The mixture was stirred at 50 °C for 15 h. The mixture was diluted with ethyl acetate (100 mL) and washed successively with water, saturated sodium bicarbonate, and brine. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 1.61 g of the methyl thioether. This material was used without further purification. To an ice-cold solution of methyl 6-[(methylthio)methyl]nicotinate (1.61 g) in methanol (35 mL) was added a solution of oxone (7.52 g) in water (35 mL). The resulting slurry was stirred at room temperature for 2 h. The resulting mixture was diluted with water (50 mL), and extracted with chloroform (3 x 100 mL). The combined organic extracts were washed with brine, dried (sodium

sulfate), filtered, and concentrated under reduced pressure to provide 1.77 g of the methyl sulfone, which was used without further purification.

To a stirred solution of methyl 6-
 5 [(methylsulfonyl)methyl]nicotinate (800 mg) in 1:1:1 tetrahydrofuran/methanol/water (30 mL) was added lithium hydroxide (440 mg). The mixture was stirred at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and
 10 chloroform (10 mL). The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with 3:1 chloroform/2-propanol (3 x 30 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 700 mg of the title
 15 compound: ^1H NMR (300 MHz, CD_3OD) δ 9.07, 8.33, 7.65, 4.77, 3.06.

Step 4: N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-
 20 [(methylsulfonyl)methyl]nicotinamide



To a stirred solution of 6-
 [(methylsulfonyl)methyl]nicotinic acid (181 mg), diisopropylethylamine (116 mg), and HBTU (341 mg) in methylene
 25 chloride (5 mL) was added a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (326 mg) and *N,N*-diisopropylethylamine (233 mg) in methylene chloride (5 mL). The mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. The residue was
 30 diluted with ethyl acetate (50 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate),

filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 to 10:90 methanol/methylene chloride) provided 165 mg of the title compound: ESI MS m/z 532 $[M + H]^+$.

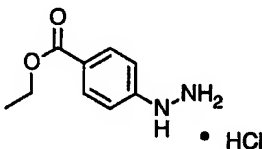
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EXAMPLE SP-225

3-Butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1H-indole-5-carboxamide

10

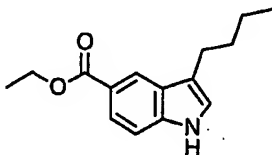
Step 1: Ethyl 4-hydrazinobenzoate hydrochloride



To a 0 °C mixture of 4-ethylaminobenzoate (10.0 g) in water (56 mL) and concentrated hydrochloric acid (20 mL) was added portion wise a solution of sodium nitrite (4.25 g) in water (20 mL). The mixture was stirred at 0 °C for 15 minutes at which time the mixture was poured into a solution of tin (II) chloride (50 gm) in water (34 mL). The resulting mixture was removed from the ice bath and allowed to slowly come to room temperature over 1 h at which time the resulting solids were collected by filtration and washed with chilled concentrated hydrochloric acid (30 mL) followed by ether. The solids were dried under vacuum to give 13 g of the title compound: ^1H NMR ($\text{DMSO}-d_6$) δ 1.29, 4.25, 7.03, 7.85, 9.0, 9.06, 10.6.

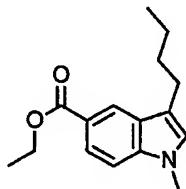
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Step 2: Ethyl 3-butyl-1H-indole-5-carboxylate



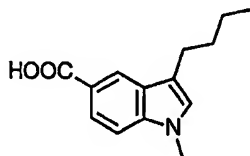
To a mixture of ethyl 4-hydrazinobenzoate hydrochloride (10 gm) in ethanol: water (5:1 100 mL) was added hexanal (4.62 gm). The mixture was refluxed at 100 °C for 3 h. The solvents were removed and toluene (100 mL) and p-toluene sulfonic acid (0.1 g) were added. The mixture was refluxed at 120 °C for 18 h, cooled to room temperature and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 90:9:1 (hexanes: methylene chloride: ethyl acetate) as eluent to give 0.8 g of the title compound: ^1H NMR (CDCl_3) δ 0.957, 1.44, 1.72, 2.78, 4.40, 7.02, 7.34, 7.90, 8.13, 8.38.

Step 3: Ethyl 3-butyl-1-methyl-1H-indole-5-carboxylate



To a mixture of ethyl 3-butyl-1H-indole-5-carboxylate (0.6 g) in methylsulfoxide (10 mL) was added potassium t-butoxide (0.29 g) and iodomethane (2.0 mL). The mixture was stirred at 50 °C for 18 H, at which time the mixture was pored into water (50 mL). The solution was extracted with ethyl acetate and the organic extracts washed three times with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% ethyl acetate in hexanes as eluent to give 0.294 g of the title compound: ^1H NMR (CDCl_3) δ 0.953, 1.44, 1.69, 2.77, 3.76, 4.40, 6.87, 7.26, 7.91, 8.35.

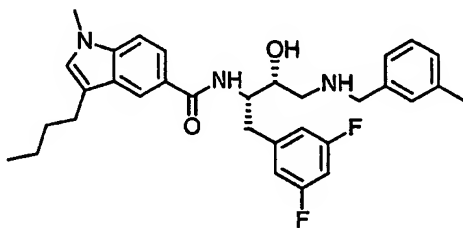
Step 4: 3-Butyl-1-methyl-1H-indole-5-carboxylic acid



To a mixture of ethyl 3-butyl-1-methyl-1H-indole-5-carboxylate (0.294 g) in methanol (20 mL) was added 1N NaOH (10 mL). The mixture was stirred at 50 °C for 18 h, cooled to room temperature and poured into 1N HCl (50 mL). The mixture
5 was extracted with ethyl acetate and the ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.234 g (89%) of the title compound: ¹H NMR (CD₃OD) δ 0.965, 1.42, 1.69, 2.76, 3.77, 7.02, 7.35, 7.84, 8.29.

10

Step 5: 3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-indole-5-carboxamide

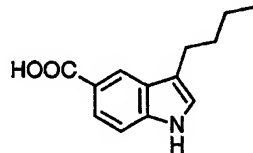


15 To a mixture of 3-Butyl-1-methyl-1H-indole-5-carboxylic acid (0.15 g) in methylene chloride (5 mL) and tetrahydrofuran (10 mL) was added 1,1-carbonyldiimidazole (0.105 g). The mixture was stirred at 40 °C at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol
20 g) in methylene chloride (5 mL) was added. The mixture was stirred at 40 °C for 18 h then poured into methylene chloride (50 mL). The mixture was washed with water then brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using
25 85:10:5 (methylene chloride: hexanes: methanol) as eluent to give 0.102 g of the title compound: MS (ESI+) for C₃₃H₃₉F₂N₃O₂ m/z 547.9 (M+H)⁺.

EXAMPLE SP-226

3-Butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1H-indole-5-carboxamide

Step 1: 3-Butyl-1H-indole-5-carboxylic acid

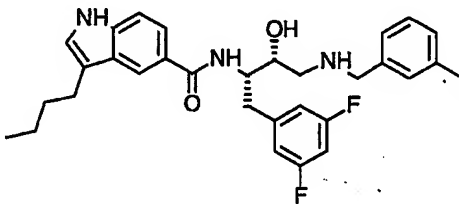


5

To a mixture of Ethyl 3-butyl-1H-indole-5-carboxylate, EXAMPLE SP-225, step2, (0.4 g) in methanol (15 mL) was added 1N NaOH (5 mL). The mixture was stirred at 50 °C for 18 h, cooled to room temperature and poured into 1N HCl (50 mL). The mixture was extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.145 g of the title compound: MS (ESI+) for $C_{13}H_{15}N_1O_2$ m/z 216.12 (M+H)⁺.

15

Step 2: 3-Butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1H-indole-5-carboxamide



20

To a mixture of 3-Butyl-1H-indole-5-carboxylic acid (0.145g) in methylene chloride (15 mL) was added triethylamine (0.068 g), and HATU (0.255 g). The mixture was stirred at room temperature for 15 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.224 g) was added. The mixture was stirred at room temperature for 72 h then poured into methylene chloride (50 mL), washed with water then saturated sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated under

25

vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride with 0.15% HOAc as eluent to give 0.247 g of the title compound: MS (ESI+) for $C_{32}H_{37}F_2N_3O_2$ m/z 534.3 (M+H)⁺.

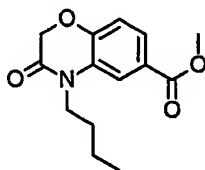
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EXAMPLE SP-227

4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

10

Step 1: Methyl 4-butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



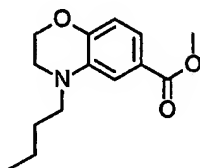
To an ice-cold, stirred solution of methyl 3-amino-4-hydroxybenzoate (3.0 g) and sodium bicarbonate (3.3 g) in 1:1 isobutyl methyl ketone/water (40 mL) was added chloroacetyl chloride (1.7 mL), and the mixture was stirred for 1 h. The mixture was warmed to room temperature and refluxed for 14 h, cooled to room temperature, diluted with chloroform, and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) afforded a phenoxazine 3.2 g as a white solid, which was used without further purification or characterization. To a solution of phenoxazine from step 1 (700 mg) and potassium carbonate (934 mg) in methanol (8 mL) was added bromobutane (1.8 mL), and the mixture was refluxed for 6 d. The mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer washed with brine, dried (magnesium sulfate),

30

filtered, and concentrated under reduced pressure to afforded 800 mg of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 7.72-7.68, 7.02-6.99, 4.66, 4.00-3.92, 1.69-1.64, 1.46-1.38, 1.01-0.95.

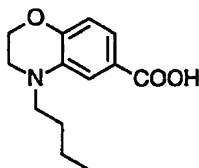
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Step 2: Methyl 4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



10 A solution of methyl 4-butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (800 mg) and 9-BBN (1.6 g) in tetrahydrofuran (13 mL) was refluxed for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.4 mL) was added, and the resulting solution was concentrated under
15 reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 25% ethyl acetate/hexanes) afforded 607 mg of the title compound: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.21, 7.16, 6.75,
20 4.24-4.21, 3.78, 3.34-3.24, 1.55-1.47, 1.38-1.30, 0.95-0.90.

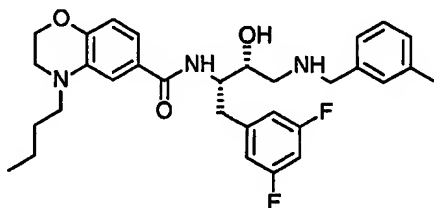
Step 3: 4-Butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid



25 To a stirred solution of methyl 4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (412 mg) in methanol (5 mL) was added 1 M potassium hydroxide (17 mL). The mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was diluted with water and

washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 50 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 384 mg of the title compound: ESI MS m/z 236 $[M + H]^+$.

Step 4: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide



10

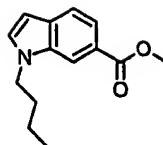
A solution of 4-Butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (43 mg), HATU (104 mg), HOBT (37 mg), and diisopropylethylamine (47 μ L) was stirred in methylene chloride (1.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (62 mg) and diisopropylethylamine (47 μ L) in methylene chloride (1.0 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 15 mg of the title compound: APCI MS m/z 552 $[M + H]^+$.

25

EXAMPLE SP-228

3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

Step 1. Methyl 1-butyl-1H-indole-6-carboxylate

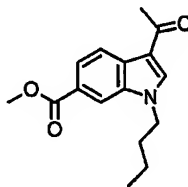


Methyl 1H-indole-6-carboxylate (4.17g) was dissolved in DMSO (30 mL), and potassium *tert*-butoxide (2.93 g) was added. The mixture was stirred for ten min at room temperature.

5 Iodobutane (3.0 mL) was added. The mixture was allowed to stir for three additional hours. The mixture was partitioned between ethyl acetate and water and brine, dried over sodium sulfate, filtered, and concentrated to give methyl 1-butyl-1H-indole-6-carboxylate (4.53 g). MS (ESI+) for $C_{14}H_{17}NO_2 + H_1$ m/z

10 232.12 (M+H)⁺.

Step 2. Methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate



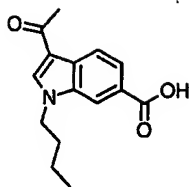
Methyl 1-butyl-1H-indole-6-carboxylate (4.53 g) was

15 dissolved in dichloromethane (25ml). The mixture was cooled to 0 °C. Diethyl aluminum chloride was added dropwise (29.5 mL) and the mixture was allowed to stir at 0 °C for 30 min. A solution of dichloromethane (25 mL) and acetyl chloride (2.1 mL) was added dropwise, and the mixture was stirred for 2 h at

20 0 °C. The mixture was then partitioned between dichloromethane, water, and brine, dried over sodium sulfate, filtered, and concentrated. The concentrate was chromatographed on silica gel using ethyl acetate/heptane (40/60) to give methyl 3-acetyl-1-butyl-1H-indole-6-

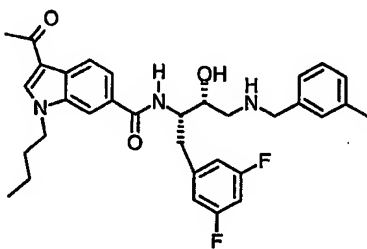
25 carboxylate (3.38 g). MS (ESI+) for $C_{16}H_{19}N_1O_3 + H_1$ m/z 274.14 (M+H)⁺.

Step 3. 3-acetyl-1-butyl-1H-indole-6-carboxylic acid



Methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate (2.00 g) was dissolved in methanol (100mL). Sodium hydroxide (1N) was added until the mixture became slightly cloudy. Methanol was again added (20 mL) until the solution was clear. Sodium hydroxide was again added until the mixture was slightly cloudy. The mixture was allowed to stir at room temperature overnight. The solution was concentrated to half its original volume and hydrochloric acid (2N) was added until the aqueous layer indicated a pH of about one. The mixture was extracted with dichloromethane and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting material was chromatographed on silica gel using MeOH/heptane/dichloromethane (4/20/76) to give 3-acetyl-1-butyl-1H-indole-6-carboxylic acid (1.60 g). MS (ESI+) for $C_{15}H_{17}N_1O_3 + H_1$ m/z 260.13 (M+H)⁺.

Step 4. 3-acetyl-1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indole-6-carboxamide



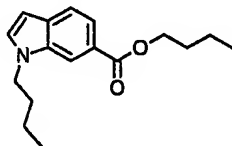
3-Acetyl-1-butyl-1H-indole-6-carboxylic acid (0.322 g) was dissolved in dichloromethane (15 mL). 1,1'-Carbonyldiimidazole was added (0.171 g). The mixture was stirred for 2 h and then a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-((3-ethylbenzyl)amino)butan-2-ol (0.250 g) in dichloromethane (15 mL) was added. After stirring

overnight, the mixture was partitioned between dichloromethane, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using MeOH/
5 dichloromethane (4/96) to give 3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide (0.335 g). MS (ESI+) for $C_{34}H_{39}F_2N_3O_3 + H_1$ m/z 576.30 (M+H)⁺.

10 EXAMPLE SP-229

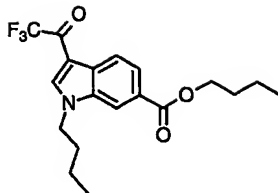
1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1H-indole-6-carboxamide

15 Step 1. Butyl 1-butyl-1H-indole-6-carboxylate



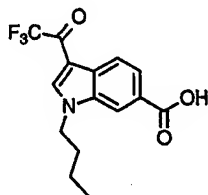
1-Butyl-1H-indole-6-carboxylic acid (0.450 g) was dissolved in dimethyl sulfoxide (10mL). Potassium tert-butoxide (0.317 g) was added and the mixture was stirred for
20 10 min at room temperature. Iodobutane (0.33 mL) was added and the mixture was allowed to stir at room temperature for 6 h. Water was then added and the mixture was partitioned between ethyl acetate, water, and brine, and dried over magnesium sulfate, filtered, and concentrated. Silica gel
25 chromatography using heptane/dichloromethane (30/70) gave butyl 1-butyl-1H-indole-6-carboxylate (0.429 g). MS (ESI+) for $C_{17}H_{23}NO_2 + H_1$ m/z 274.20 (M+H)⁺.

Step 2. Butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-
30 carboxylate



Boron trifluoride-methyl sulfide complex (0.238 g) was dissolved in dichloromethane (10 mL). The solution was cooled to -78 °C and a solution of trifluoroacetic anhydride (0.384 g) in dichloromethane (2 mL) was added. The mixture was stirred at -78 °C for 10 min, at which time a solution of butyl 1-butyl-1H-indole-6-carboxylate (0.250 g) in dichloromethane (3 mL) was added. The mixture was allowed to stir at -78 °C for 15 min and then allowed to warm to room temperature overnight. The mixture was then poured into aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated and the resulting material was chromatographed on silica gel using ethyl acetate/heptane (20/80) to give butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylate (0.302 g). MS (ESI+) for $C_{19}H_{22}F_3N_1O_3 + H_1$ m/z 370.16 (M+H)⁺.

Step 3. 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid



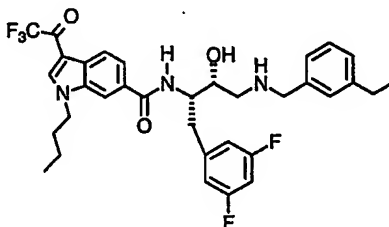
20

Butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylate (0.277 g), LiOH·H₂O (0.040 g), THF (1.5 mL), water (0.5 mL), and methanol (0.5 mL) were stirred overnight at room temperature. The solvents were then removed under reduced pressure and HCl (2N, 0.5mL) was added to the residue. The residue was extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica

25

gel using methanol/dichloromethane (6/94) gave 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid (0.166 g). MS (ESI+) for $C_{15}H_{14}F_3N_1O_3+H_1$ m/z 314.10 $(M+H)^+$.

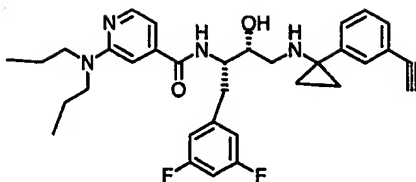
- 5 Step 4. 1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(trifluoroacetyl)-1H-indole-6-carboxamide



- 1-Butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid
 10 (0.141 g) was dissolved in dichloromethane (10 mL). 1,1'-Carbonyldiimidazole (0.080 g) was added and the mixture was stirred at room temperature for 2 h. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.166 g) in dichloromethane was added and the mixture was
 15 allowed to stir overnight at room temperature. The mixture was then partitioned between dichloromethane and water, dried over sodium sulfate, filtered, and concentrated. Chromatography on silica gel using methanol/ethyl acetate/heptane /dichloromethane (3/10/10/77 to 6/10/10/74)
 20 gave 1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(trifluoroacetyl)-1H-indole-6-carboxamide (0.155 g). MS (ESI+) for $C_{34}H_{36}F_5N_3O_3+H_1$ m/z 630.28 $(M+H)^+$.

25 EXAMPLE SP-230

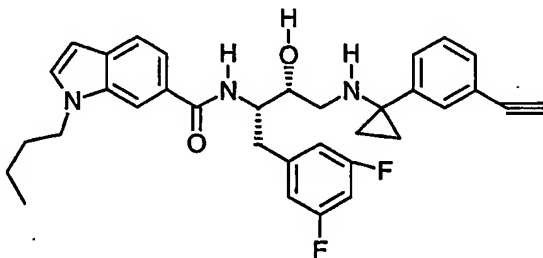
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide



2-(Dipropylamino)isonicotinic acid (0.206 g) was dissolved in dichloromethane (10 mL). 1,1'-Carbonyldiimidazole was added (0.142 g) and the mixture was stirred for 2 h at room temperature, at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-([1-(3-ethynylphenyl)cyclopropyl]amino)butan-2-ol (0.284 g) in dichloromethane was added. The mixture was allowed to stir overnight and then was partitioned between dichloromethane, water, and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was chromatographed on silica gel using methanol/dichloromethane (4/96) to give N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide (0.268g). MS (ESI+) for $C_{33}H_{38}F_2N_4O_2 + H_1$ m/z 561.30 (M+H)⁺.

EXAMPLE SP-231

1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-1H-indole-6-carboxamide



In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide, 1-butyl-1H-indole-6-carboxylic acid (0.119 g) gave 1-butyl-N-((1S,2R)-1-

(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-1H-indole-6-carboxamide (0.076g). MS (ESI+) for $C_{34}H_{35}F_2N_3O_2+H_1$ m/z 556.28 (M+H)⁺.

5

EXAMPLE SP-231

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)benzamide

10

Step 1. 3-(Allylthio)benzoic acid

3-Thiobenzoic acid (Aldrich, 4.3g, 28mmol) was dissolved in THF (100mL), cooled to 0°C, and treated with KO-tBu (6.3g, 56mmol), followed by allyl bromide (2.4mL, 28mmol). The solvent was removed from the reaction mixture and the residue was partitioned between 3M HCl and EtOAc. The organic layer was separated, dried (MgSO₄) and concentrated to give the title compound (5.3g). (LRMS (M-H) m/z 193.2)

15

Step 2. 3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-

3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)benzamide

20

3-(Allylthio)benzoic acid (717mg, 3.69mmol), (2R,3R)-3-amino-4-(3,5-difluorophenyl)-1-([1-(3-ethylphenyl)cyclopropyl]amino)butan-2-ol (247mg, 0.685mmol), and HATU (Aldrich, 2.1g, 5.54mmol) were dissolved in dichloromethane (35mL), at ambient temperature, and treated with diisopropylethylamine (1.6mL, 9.225mmol). Upon completion, the reaction mixture was concentrated and chromatographed (SiO₂, 2:1 to 1:1 Hexanes: EtOAc) to give the desired compound (650mg). (LRMS (M+H) m/z =537.8)

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EXAMPLE SP-232

3-(allylsulfinyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide
5 (325mg, 0.606mmol) was dissolved in CH₂Cl₂ (10mL) and AcOH (1mL) and treated with mCPBA (104mg, 0.606mmol). The reaction mixture was stirred for 2.5h, at which time more mCPBA (20mg, 0.11mmol) was added and stirring continued for 30 min. more.
10 The organic layer was diluted with Et₂O and washed with 15% sodium thiosulfite solution. The organic was washed with brine, then dried (MgSO₄) and concentrated to give an oil, which was chromatographed with 25% to 50% EtOAc in hexanes to give the title compound. (LRMS (M+H) m/z 553.8)

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EXAMPLE SP-233

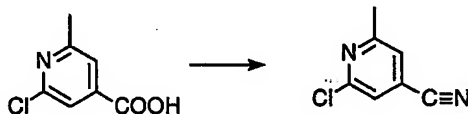
3-(allylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)benzamide

5 3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)benzamide (245mg, 0.456mmol) was dissolved in MeOH:H₂O (9:1, 6mL) and treated with oxone (561mg, 0.913mmol). When the reaction was complete, the mixture was concentrated to 0.5x volume and poured onto EtOAc. This was washed with a 15% sodium thiosulfite solution, dried (MgSO₄) and concentrated to give the title compound. (LRMS (M+H) m/z 569.8)

EXAMPLE SP-234

15 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylisonicotinamide

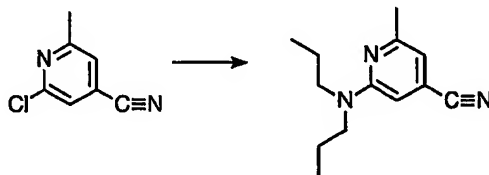
Step 1. 2-chloro-6-methylisonicotinonitrile



20

Using the method of Org. Prep. Proceed. Intern. (1982) 396, 2-chloro-6-methylisonicotinic acid (0.405 g, 2.36 mmol) was converted to 2-chloro-6-methylisonicotinonitrile (0.241 g).

Step 2. 2-(dipropylamino)-6-methylisonicotinonitrile

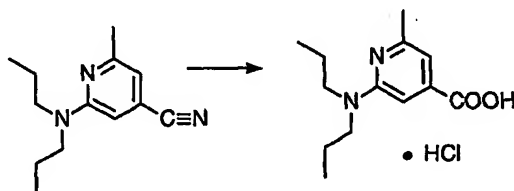


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To 2-chloro-6-methylisonicotinonitrile (0.230 g, 1.51 mmol) was added di-n-propylamine (5 mL). The mixture was heated at 80 °C in a sealed, thick-walled glass vessel for 12 h and then at room temperature for 17 h. Excess di-n-

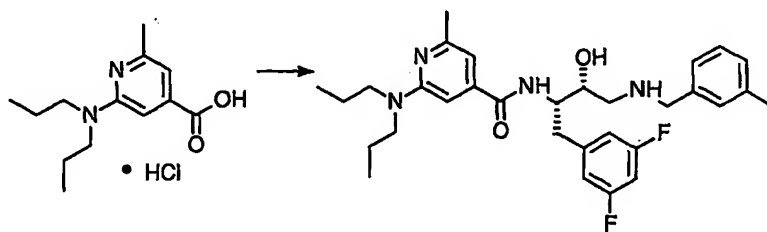
propylamine was removed under reduced pressure and the residue was partitioned between dichloromethane and aq. sodium bicarbonate. After drying over sodium sulfate and concentration, the residue was chromatographed on silica gel using ethyl acetate-hexane (10/90) to give 0.14 g of 2-chloro-6-methylisonicotinonitrile and 0.059 g of 2-(dipropylamino)-6-methylisonicotinonitrile. Using the above conditions, 2-chloro-6-methylisonicotinonitrile (0.14 g) was converted to an additional 0.043 g of 2-(dipropylamino)-6-methylisonicotinonitrile.

Step 3. 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride



To 2-(dipropylamino)-6-methylisonicotinonitrile (0.094 g, 0.433 mmol) was added 4N HCl (2 mL) and THF (1 mL). The mixture was stirred at 100 °C (THF allowed to distill off) for 12 h, then the aqueous layer was removed under reduced pressure and using a toluene azeotrope to give 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride, which was used without further purification in the next step.

Step 4. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(dipropylamino)-6-methylisonicotinamide



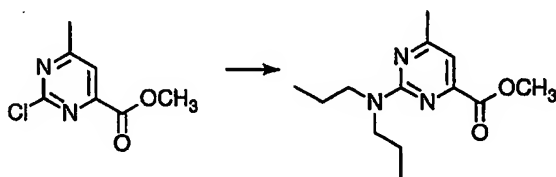
To 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride (approx. 0.4 mmol) in THF (3 mL) was added

triethylamine (0.17 mL), followed by dichloromethane (2 mL) and then CDI (0.071 g, 0.44 mmol). After stirring for 1 h, a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (0.163 g, 0.400 mmol), triethylamine (0.11 mL), and dichloromethane (approx. 2 mL) was added to the CDI mixture. The mixture was allowed to stir overnight, after which an additional 0.12 mL of triethylamine and 0.045 g of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride was added. After stirring for several more hours, the mixture was partitioned between dichloromethane and aq. sodium bicarbonate. The organic layer was dried with sodium sulfate, concentrated, and the residue was chromatographed on silica gel using MeOH-dichloromethane (5/95) to give 0.04 g of the title compound.

EXAMPLE SP-235

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide

Step 1. methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate

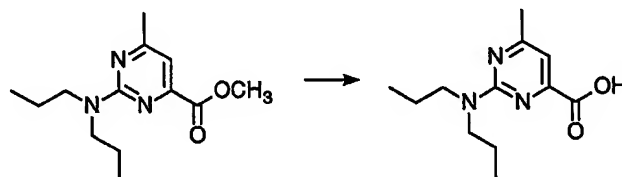


A mixture of methyl 2-chloro-6-methylpyrimidine-4-carboxylate (0.411 g, 2.20 mmol), di-n-propylamine (0.668 g, 6.60 mmol), triethylamine (0.267 g, 2.64 mmol), and THF (5 mL) was stirred at room temperature for 55 min and then at reflux for 1.3 h, at which time it was cooled and partitioned between ethyl acetate and a mixture of brine and aq. sodium bicarbonate. The organic layer was dried over magnesium

sulfate and concentrated and then chromatographed on silica gel using ethyl acetate-hexane (90/10) to give methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate (0.457 g) as a pale yellow liquid.

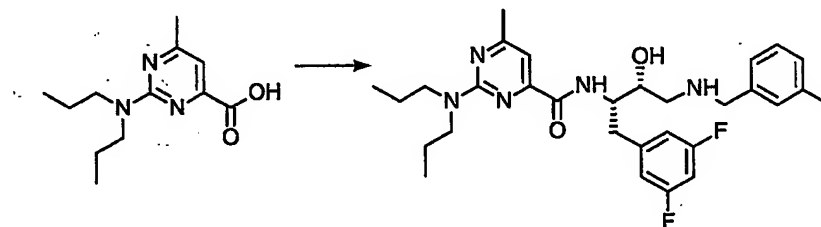
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Step 2. 35137-ret-135 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid



To methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate (0.450 g, 1.79 mmol) in MeOH (2 mL), water (1 mL), and THF (1 mL) was added lithium hydroxide monohydrate (0.113 g, 2.68 mmol). The mixture was stirred at room temperature for 1 h and then MeOH and THF were removed under reduced pressure. The pH of the residue was adjusted to approximately 5 and the resulting mixture was extracted with dichloromethane, dried over sodium sulfate, and concentrated to give 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid (0.351 g) as a yellow solid.

20 Step 3. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide



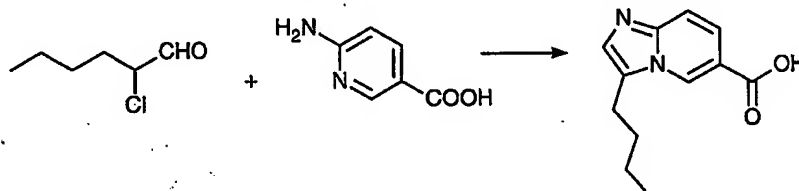
To 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid (0.101 g, 0.426 mmol) in THF (0.5 mL) was added 1,1'-carbonyldiimidazole (CDI) (0.076 g, 0.468 mmol). After 50 min the CDI mixture was added to a mixture of (2R,3S)-3-amino-4-

(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (0.173 g, 0.425 mmol) and triethylamine (0.18 mL, 1.28 mmol) in THF (6 mL) and dichloromethane (2 mL). After stirring overnight, the solvents were removed under reduced pressure and the residue was partitioned between dichloromethane, aq. sodium bicarbonate, and aq. sodium bicarbonate-brine mixture. The organic layer was dried over sodium sulfate, concentrated, and the residue was chromatographed on silica gel using MeOH-dichloromethane (5/95) to give 0.199 g of the title compound as a solid.

EXAMPLE SP-236

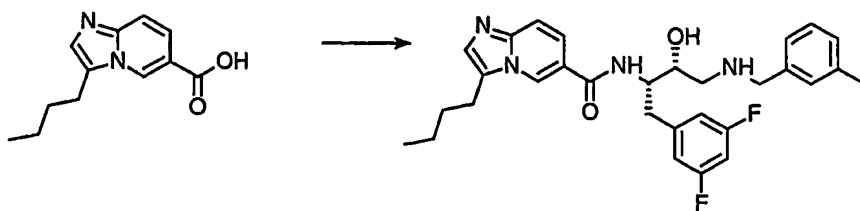
3-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]imidazo[1,2-a]pyridine-6-carboxamide

Step 1. 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid



To hexanal (1.02 g, 10.2 mmol) in 15 mL of isopropyl alcohol-water (4:1 v/v) was added CuCl_2 (1.37 g, 10.2 mmol). The mixture was heated at 80 °C for 2.5 h, then cooled. The solids were removed by filtration and the filtrate was added to 6-aminonicotinic acid (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature, then heated at reflux 32 h. After cooling, the solvents were removed under reduced pressure and MeOH was added to the residue. The resulting solid was removed by filtration and the filtrate was concentrated to dryness. MeOH was again added, and the resulting solid removed by filtration. After concentration of the filtrate, the residue was chromatographed on silica gel using MeOH-dichloromethane (33/67) to give 0.26 g of 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid.

3-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)imidazo[1,2-a]pyridine-6-carboxamide



- 5 Step 2. In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-SP-235}, Step 3, 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid (0.16 g) was converted to 0.30 g of the title compound.

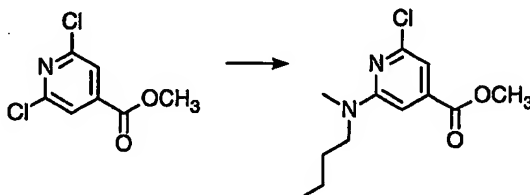
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EXAMPLE SP-237

2-[butyl(methyl)amino]-6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide

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Step 1. methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate

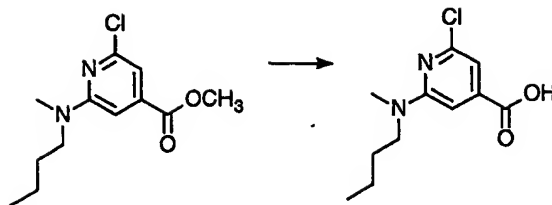


- In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylisonicotinamide {EXAMPLE SP-234, Step 2,} methyl 2,6-dichloroisonicotinate (1.0 g) was converted to methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.87 g)..

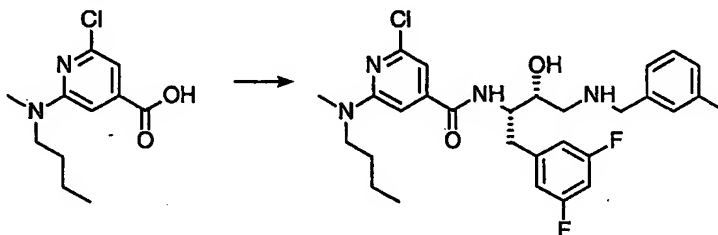
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Step 2. 2-[butyl(methyl)amino]-6-chloroisonicotinic acid

25



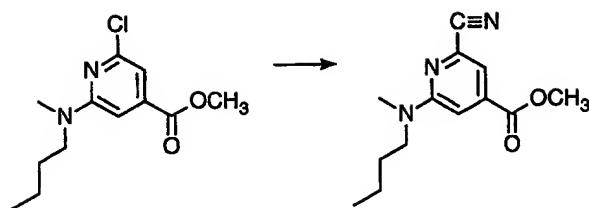
- In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 2, methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.17 g) was converted to 2-[butyl(methyl)amino]-6-chloroisonicotinic acid (0.15 g).
- Step 3. 2-[butyl(methyl)amino]-6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide



- In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 3, 2-[butyl(methyl)amino]-6-chloroisonicotinic acid (0.15 g) was converted to 0.13 g of the title compound.

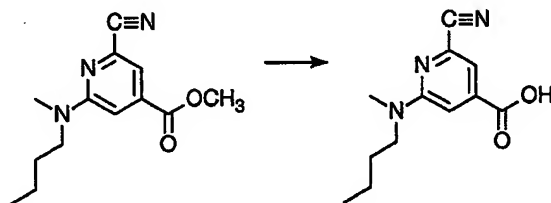
20 EXAMPLE SP-238

- 2-[butyl(methyl)amino]-6-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide
- Step 1. methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate



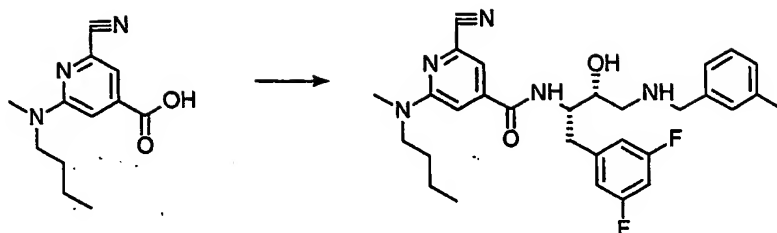
A flask containing methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.306 g, 1.19 mmol), zinc cyanide (0.0839 g, 0.714 mmol), Pd₂dba₃ (0.0218 g, 0.024 mmol), dppf (0.0264 g, 0.048 mmol), and zinc dust (0.0093 g, 0.143 g) was flushed with nitrogen. N-Methylpyrrolidinone (2 mL) was added and the mixture was heated at 120 °C for 2 h, at which time it was cooled and partitioned between ethyl acetate and aq. ammonium hydroxide and brine. The organic layer was dried over magnesium sulfate and concentrated, followed by silica gel chromatography using ethyl acetate-hexane (10/90) to give 0.161 g of methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate.

Step 2. 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid



In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 2, methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate (0.157 g) was converted to 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid (0.151 g).

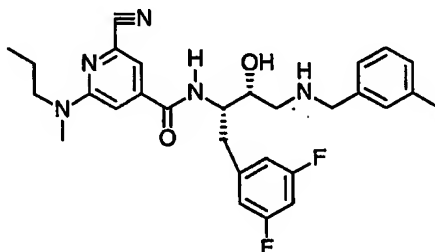
Step 3. 2-[butyl(methyl)amino]-6-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-
 5 2435}, Step 3, 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid (0.135 g) was converted to the title compound (0.223 g).

EXAMPLE SP-239

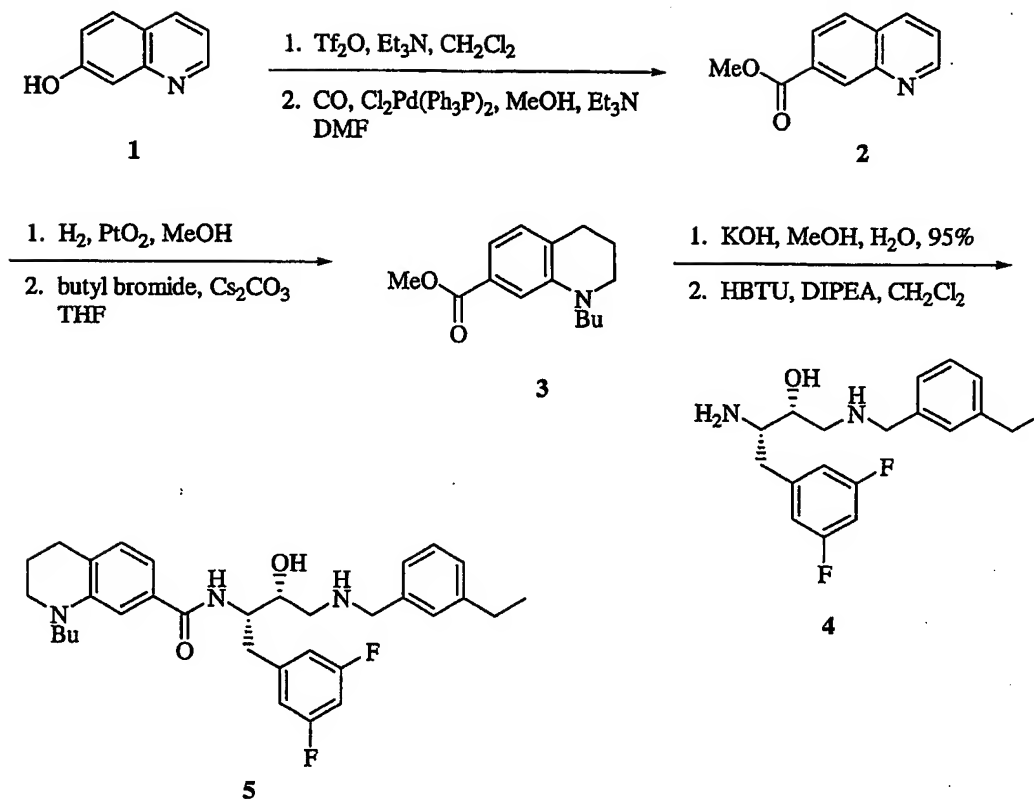
2-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
 10 ethylbenzyl)amino]-2-hydroxypropyl}-6-[methyl(propyl)amino]isonicotinamide



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-
 15 2435}, Step 3, 2-cyano-6-[methyl(propyl)amino]isonicotinic acid (0.13 g) gave 0.23 g of the title compound.

20 EXAMPLE SP-240

Reaction scheme for the preparation of 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoline-7-carboxamide



1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

Step 1: To an ice-cold, stirred solution of quinolin-7-ol (1.0 g, 6.9 mmol) and triethylamine (1.0 mL, 7.6 mmol) in methylene chloride (14 mL) was added trifluoromethane sulfonic anhydride (1.3 mL, 7.6 mmol), and the mixture was stirred for 30 min. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure provided quinolin-7-yl trifluoroacetate (1.5 g): ESI MS m/z 278 $[\text{M} + \text{H}]^+$.

Step 2: To a stirred solution of quinolin-7-yl trifluoroacetate (750 mg, 2.7 mmol), $\text{PdCl}_2(\text{Ph}_3\text{P})$ (95 mg, 0.14 mmol), and triethylamine (1.2 mL, 8.4 mmol) in 1:2 DMF/MeOH

(39 mL) was degassed and sparged with CO, and the mixture was heated at 60 °C for 48 h. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. The residue was diluted
5 with a 5% solution of LiCl, and washed with CHCl₃ (3 x 250 mL). The combined organics were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 3:1 ethyl acetate/hexanes) provided methyl quinoline-7-carboxylate (185 mg): ESI MS m/z
10 188 [M + H]⁺.

Step 3: A solution of methyl quinoline-7-carboxylate (185 mg, 1.0 mmol) and PtO₂ (20 mg) in methanol (10 mL) was shaken under an atmosphere of hydrogen for 2 h. The reaction mixture was
15 filtered through diatomaceous earth, and concentrated under reduced pressure to provide methyl 1,2,3,4-tetrahydroquinoline-7-carboxylate (189 mg): ESI MS m/z 192 [M + H]⁺.

20 Step 4: To a stirred solution of methyl 1,2,3,4-tetrahydroquinoline-7-carboxylate (180 mg, 0.94 mmol) and cesium bicarbonate (1.5 g, 4.7 mmol) in THF (2 mL) was added n-butyl bromide (1.0 mL, 9.4 mmol), and the reaction mixture was heated at reflux for 48 h. The reaction mixture was
25 cooled to room temperature, and diluted with EtOAc. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:3 ethyl acetate/hexanes) afforded methyl 1-butyl-
30 1,2,3,4-tetrahydroquinoline-7-carboxylate (156 mg): ESI MS m/z 248 [M + H]⁺.

Step 5: To a stirred solution of methyl 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylate (156 mg, 0.63 mmol) in

methanol (1.3 mL) was added potassium hydroxide (6.3 mL of a 1 M solution in water, 6.3 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) afforded 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylic acid (139 mg): ESI MS m/z 234 $[M + H]^+$.

Step 6: A solution of 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylic acid (134 mg, 0.57 mmol), HBTU (327 mg, 0.86 mmol), and diisopropylethylamine (150 μ L, 0.86 mmol) was stirred in methylene chloride (3.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (EXAMPLE SP-272) (234 mg, 0.57 mmol) and diisopropylethylamine (150 μ L, 0.86 mmol) in methylene chloride (3.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 1-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1,2,3,4-tetrahydroquinoline-7-carboxamide (130 mg): ESI MS m/z 550 $[M + H]^+$

EXAMPLE SP-241

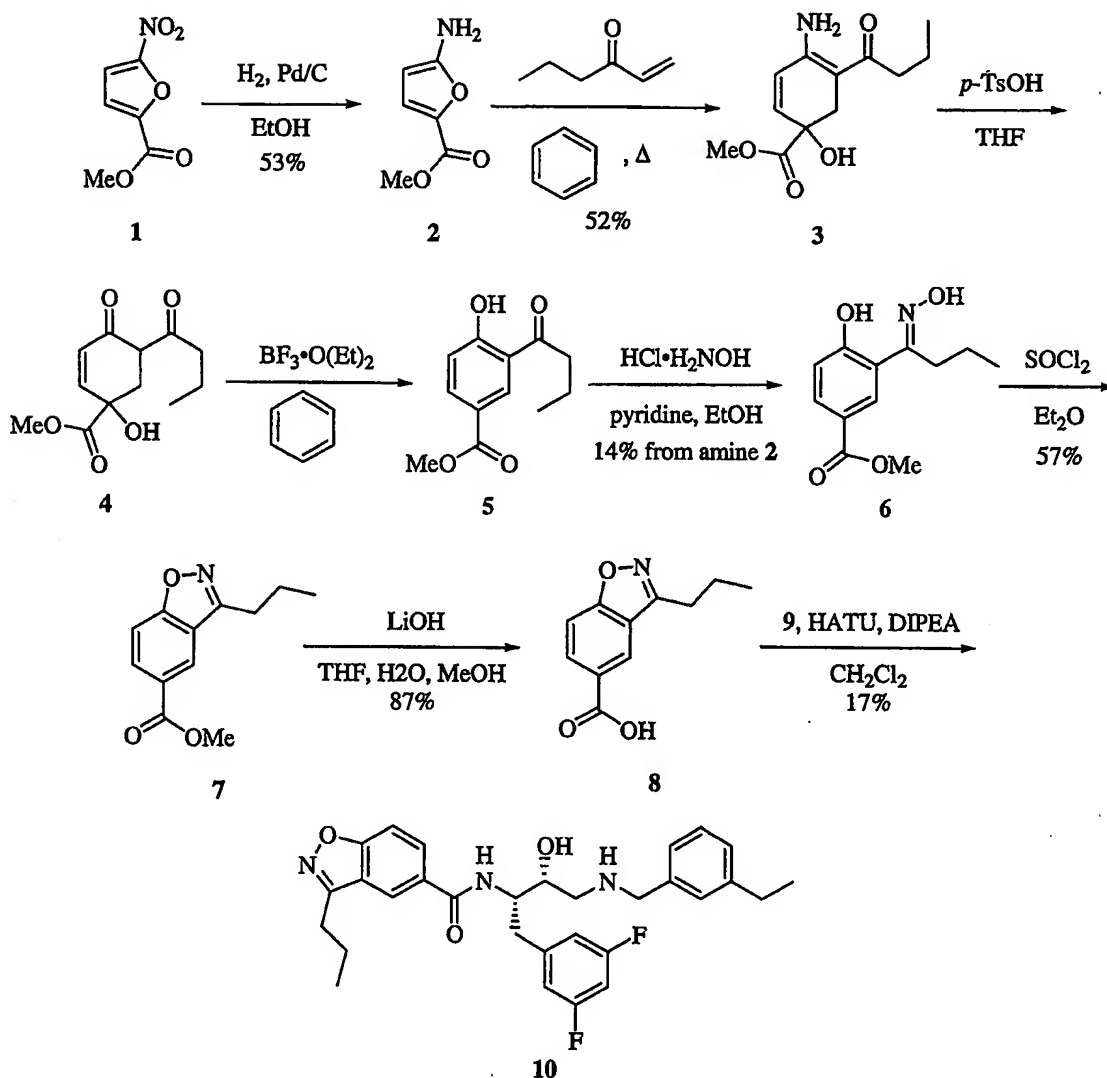
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-propyl-1,2-benzisoxazole-5-carboxamide

General Synthesis of Benzisoxazole

5 Furan **1** was hydrogenated to afford amine **2**. Diels-Alder reaction of amine **2** and 1-hexen-3-one afforded ketone **3**.¹ Ketone **3** was then treated with p-toluenesulfonic acid to afford diketone **4**. Diketone **4** was rearomatized with boron trifluoride to give phenol **5**. Phenol **5** was then converted to
10 oxime **6** with hydroxylamine. Oxime **6** was cyclized with thionyl chloride to afford methyl ester **7**.² Methyl ester **7** was then saponified to acid **8**. Coupling of acid **8** and amine **9** in the presence of HATU, provided benzoxazole **10**.

15

Reaction scheme



N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-propyl-1,2-benzisoxazole-5-carboxamide

- 5 Step 1: A mixture of methyl 5-nitro-2-furoate (13 g, 76 mmol) and 10% Pd/C (1.3 g) in ethanol (150 mL) was shaken under an atmosphere of hydrogen at 40 psi for 18 h. The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to afford a crude oil.
- 10 Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) provided methyl 5-amino-2-furoate (5.6 g): ^1H NMR (500 MHz, CDCl_3) δ 7.11–7.10 (m, 1H), 5.31–5.29 (m, 1H), 4.31 (br s, 2H), 3.84 (s, 3H).

Step 2: A stirred solution of methyl 5-amino-2-furoate (1.4 g, 10 mmol) and 1-hexen-3-one (7 mL, 60 mmol) in benzene (50 mL) was heated to reflux for 2 h. The reaction mixture was concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 2:1 hexanes/ethyl acetate) provided methyl 4-amino-5-butyryl-1-hydroxycyclohexa-2,4-diene-1-carboxylate (1.25 g): ¹H NMR (300 MHz, CDCl₃): δ 6.26-6.23 (m, 1H), 6.09-6.05 (m, 1H), 3.80 (s, 3H), 3.02-2.96 (m, 1H), 2.89-2.84 (m, 1H), 2.42-2.37 (m, 2H), 1.64-1.57 (m, 2H), 0.96-0.88 (m, 3H).

Step 3: To a stirred solution of methyl 4-amino-5-butyryl-1-hydroxycyclohexa-2,4-diene-1-carboxylate (1.25 g, 5.2 mmol) in a 1:1 mixture of water/tetrahydrofuran (10 mL) was added p-toluenesulfonic acid monohydrate (1.1 g, 5.8 mmol). The reaction mixture was stirred for 18 h and then partitioned between dichloromethane and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 5-butyryl-1-hydroxy-4-oxocyclohex-2-ene-1-carboxylate which was used without further purification or characterization.

Step 4: To a stirred solution of methyl 5-butyryl-1-hydroxy-4-oxocyclohex-2-ene-1-carboxylate in benzene was added BF₃·O(Et)₂ (1.3 mL, 10 mmol). The mixture was stirred for 0.25 h and then quenched with saturated sodium bicarbonate followed by extraction with dichloromethane. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 3-butyryl-4-hydroxybenzoate which was used without further purification or characterization.

Step 5: A stirred solution of methyl 3-butyryl-4-hydroxybenzoate, pyridine (3.7 mL, 46 mmol), and hydroxylamine

hydrochloride (3.55 g, 51 mmol) in ethanol (30 mL) was heated reflux for 2 h. The mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 10:1 hexanes/ethyl acetate) provided methyl 4-hydroxy-3-[(1E)-N-hydroxybutanimidoyl]benzoate (170 mg): ¹H NMR (500 MHz, CD₃OD):

10 δ 8.30-8.28 (m, 1H), 7.85-7.82 (m, 1H), 6.92-6.89 (m, 1H), 3.88 (s, 3H), 2.87-2.84 (m, 2H), 1.67-1.60 (m, 2H), 1.05-1.00 (m, 3H).

Step 6: To an ice-cold stirred solution of methyl 4-hydroxy-3-[(1E)-N-hydroxybutanimidoyl]benzoate (170 mg, 0.7 mmol) in diethyl ether (5 mL) was added a mixture of thionyl chloride (60 μL, 0.8 mmol) and pyridine (580 μL, 7.2 mmol) in diethyl ether (5 mL). After 2.5 h the mixture was poured over ice-water and acidified to pH = 1 with 1 N hydrochloric acid. The mixture was then partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 10:1 hexanes/ethyl acetate) provided methyl 3-propyl-1,2-benzisoxazole-5-carboxylate (90 mg): ¹H NMR (300 MHz, CDCl₃): δ

25 8.36-8.35 (m, 1H), 8.07-8.04 (m, 1H), 7.52-7.49 (m, 1H), 3.95 (s, 3H), 2.96-2.91 (m, 2H), 2.00-1.87 (m, 2H), 1.09-1.04 (m, 3H).

30

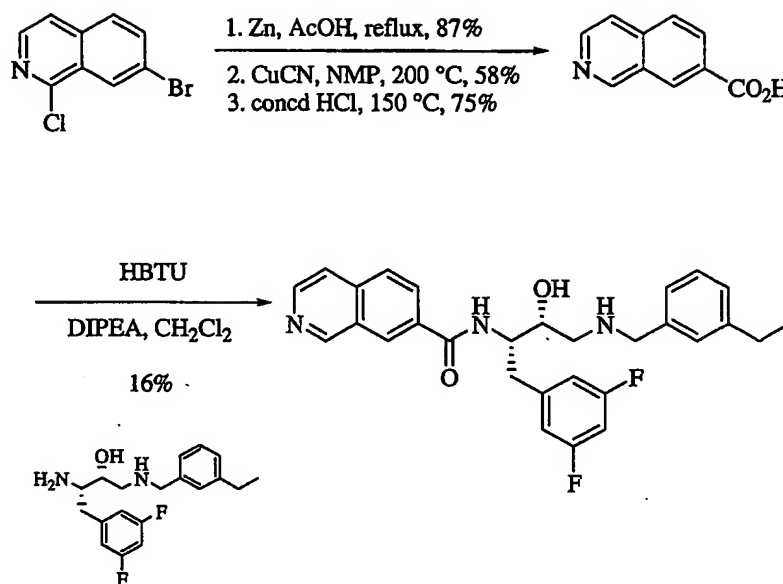
Step 7: To a solution of methyl 3-propyl-1,2-benzisoxazole-5-carboxylate (90 mg, 0.4 mmol) in a 2:1:1 mixture of tetrahydrofuran, water, and methanol (4 mL) was added lithium hydroxide (50 mg, 1.2 mmol) and the resulting reaction mixture

stirred at room temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure, and partitioned between water and ethyl ether. The aqueous layer was washed twice with ether and acidified to pH 1 with 6 M hydrochloric acid. The resulting aqueous layer was extracted with ethyl acetate, dried (sodium sulfate), and concentrated under reduced pressure to afford 3-propyl-1,2-benzisoxazole-5-carboxylic acid (73 mg): ¹H NMR (300 MHz, CD₃OD): δ 8.28-8.27 (m, 1H), 8.09-8.06 (m, 1H), 7.64-7.61 (m, 1H), 2.99-2.94 (m, 2H), 1.96-1.86 (m, 2H), 1.08-1.02 (m, 3H).

Step 8: To a stirred solution of 3-propyl-1,2-benzisoxazole-5-carboxylic acid (70 mg, 0.3 mmol) and HATU (130 mg, 0.3 mmol) in methylene chloride (5 mL) was added *N,N*-diisopropylethylamine (110 μL, 0.6 mmol). In a separate flask, *N,N*-diisopropylethylamine (110 μL, 0.6 mmol) was added to (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (EXA xxx) (140 mg, 0.3 mmol) in methylene chloride (2 mL). This solution was added to the above solution containing the acid and the resulting reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, gradient 97:3 to 94:6 methylene chloride/methanol) provided *N*-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-propyl-1,2-benzisoxazole-5-carboxamide (30 mg). ESI-MS *m/z* 522 [*M* + *H*]⁺

EXAMPLE SP-242

N-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide dihydrochloride



Step 1: A solution of 7-bromo-1-chloroisoquinoline (2.50 g, 10.3 mmol) and activated zinc (1.40 g, 21.65 mmol) in acetic acid (20 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 7-bromoisoquinoline (1.86 g): ESI MS m/z 208 [M + H]⁺.

Step 2: A solution of 7-bromoisoquinoline (1.80 g, 8.65 mmol) and cuprous cyanide (1.16 g, 12.97 mmol) in *N*-methyl pyrrolidinone (17 mL) was heated to 200 °C for 2 h. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous phase was back-extracted with additional ethyl acetate and the combined organic layers were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 7-cyano-isoquinoline (770 mg): ¹H NMR (300 MHz, CDCl₃) δ 9.35 (s, 1H), 8.70 (d, *J* = 5 Hz, 1H),

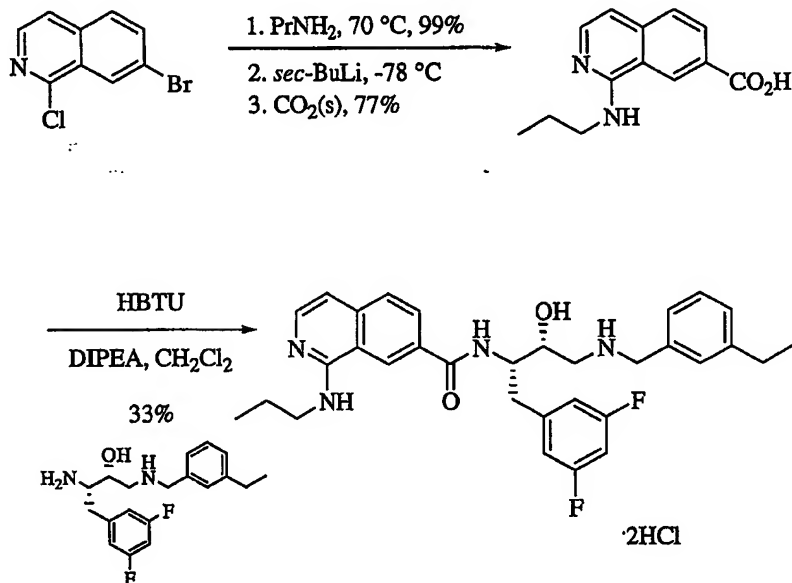
8.40 (s, 1H), 7.95 (d, $J = 8$ Hz, 1H), 7.84 (d, $J = 8$ Hz, 1H), 7.73 (d, $J = 5$ Hz, 1H); ESI MS m/z 155 $[M + H]^+$.

Step 3: A solution of 7-cyanoisoquinoline (770 mg, 5.0 mmol) in concentrated hydrochloric acid (25 mL) was heated in a sealed tube to 150 °C for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (10 mL) and neutralized to pH 7.0 with concentrated ammonium hydroxide. The solution was vacuum filtered and the filtrate concentrated under reduced pressure to provide isoquinoline-7-carboxylic acid (640 mg): ESI MS m/z 174 $[M + H]^+$.

Step 4: To a stirred solution of isoquinoline-7-carboxylic acid (200 mg, 1.15 mmol) and *N,N*-diisopropyl ethylamine (1.20 mL, 6.88 mmol) in methylene chloride (14.0 mL) was added HBTU (438 mg, 1.15 mmol) and the reaction stirred for 0.5 h. (2*R*,3*S*)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (470 mg, 1.15 mmol) was added in one portion and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 0-5% methanol/methylene chloride) gave *N*-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide (100 mg) which was characterized as its bis-HCl salt: mp 142-143 °C; ESI MS m/z 490 $[M + H]^+$

EXAMPLE SP-243

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamide dihydrochloride



5

Step 1: A solution of 7-bromo-1-chloroisoquinoline in propylamine (15.0 mL) was heated at 70 °C in a sealed tube overnight. The reaction mixture was concentrated under reduced pressure, then dissolved in chloroform and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 7-bromo-2-(N-propylamino)isoquinoline (820 mg): ESI MS m/z 266 $[\text{M} + \text{H}]^+$.

15

Step 2: A solution of 7-bromo-2-(N-propylamino)isoquinoline (200 mg, 0.754 mmol) in anhydrous diethyl ether (1.0 mL) was cooled to -65 °C. To this solution *sec*-butyllithium was added dropwise (1.30 mL of a 1.3 M solution in cyclohexane, 1.69 mmol) and the reaction mixture stirred at -60 °C for 10 min. The reaction mixture was quenched by addition of pulverized dry ice (CO_2) and the reaction allowed to slowly warm to room temperature over 1 h. The resulting solution was acidified

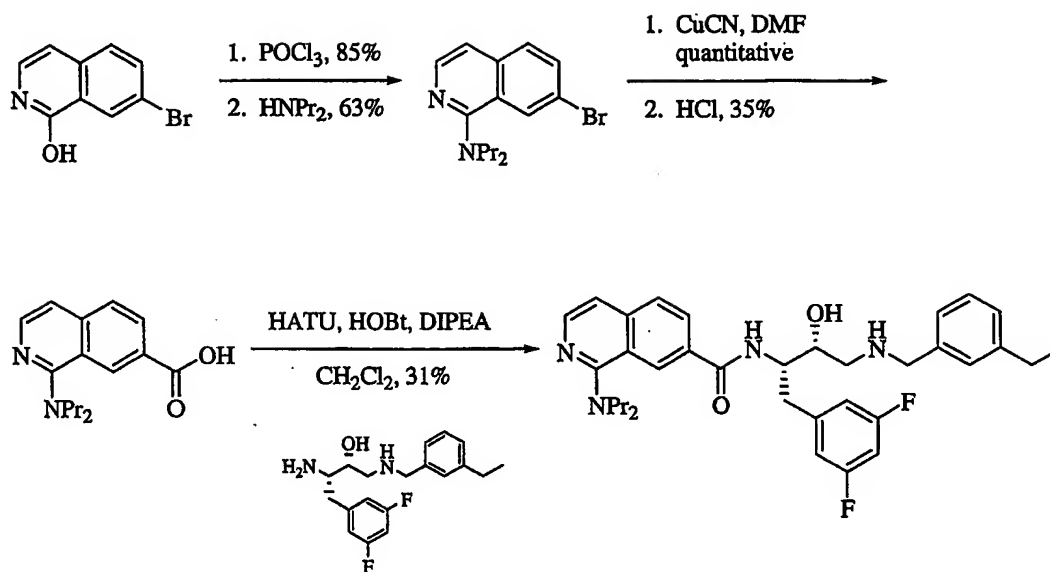
with 1 N hydrochloric acid and the reaction mixture extracted with ethyl acetate (3 x 15 mL). The combined organic phase was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown solid.

5 Purification by flash column chromatography (silica, 66:20:10:4 ethyl acetate/chloroform/methanol/concentrated ammonium hydroxide) gave 1-(propylamino)isoquinoline-7-carboxylic acid (133 mg): ESI MS m/z 231 $[M + H]^+$.

10 Step 3: To a stirred solution of 1-(propylamino)isoquinoline-7-carboxylic acid (81 mg, 0.396 mmol) and *N,N*-diisopropyl ethylamine (3.75 μ L, 2.16 mmol) in methylene chloride (5.0 mL) was added HBTU (152 mg, 0.396 mmol) and the reaction stirred for 0.5 h. (2*R*,3*S*)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (150 mg, 0.36 mmol) was added in
15 one portion and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium
20 sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 0-5% methanol/methylene chloride) gave *N*-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamide (67 mg) which was
25 characterized as its bis-HCl salt: mp 262 °C dec; ESI MS m/z 547 $[M + H]^+$

EXAMPLE SP-244

N-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-
30 hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide



Step 1: A solution of 7-bromoisoquinolin-1-ol (2.5 g, 11.1 mmol) and POCl_3 (10.4 mL, 111 mmol) was stirred at 70 °C for 2.5 h. The reaction mixture was cooled to room temperature, poured into ice water, and the solution was stirred overnight. The aqueous mixture was diluted with chloroform, washed with a saturated solution of NaHCO_3 , saturated NaCl , dried (MgSO_4), filtered, and concentrated under reduced pressure to afford 7-bromo-1-chloroisoquinoline (2.3 g): ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.39-8.36 (m, 2H), 8.09-8.02 (m, 2H), 7.95 (d, $J = 6$ Hz, 1H).

Step 2: A solution of 7-bromo-1-chloroisoquinoline from step 1 (500 mg, 2.1 mmol) and dipropylamine (2.8 mL, 21 mmol) was heated at 150 °C in a sealed tube for 2 d. The reaction mixture was cooled, and the solvent was removed under reduced pressure to provide 7-bromo-N,N-dipropylisoquinolin-1-amine (400 mg): ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.55 (s, 1H), 7.90 (d, $J = 6$ Hz, 1H), 7.75-7.64 (m, 2H), 6.87 (d, $J = 6$ Hz, 1H), 3.42 (q, $J = 7$ Hz, 4H), 1.65 (q, $J = 7$ Hz, 4H), 0.94 (t, $J = 7$ Hz, 6H).

Step 3: A solution of 7-bromo-N,N-dipropylisoquinolin-1-amine (350 mg, 1.1 mmol) and CuCN (204 mg, 2.2 mmol) in N,N-dimethylformamide (2 mL) was stirred at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with
5 water, and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide 1-(dipropylamino)isoquinoline-7-carbonitrile (279 mg, which was used without any further
10 characterization.

Step 4: A solution of 1-(dipropylamino)isoquinoline-7-carbonitrile from step 3 (279 mg, 1.1 mmol) in concentrated hydrochloric acid (4 mL) was heated at 150 °C in a sealed tube
15 for 14 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in a 25% ammonium hydroxide/water solution and stirred for 1 h. The solution was acidified to pH 4 with concentrated hydrochloric acid, and
20 extracted with chloroform (3 x 50 mL). The combined organics were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to provide 1-(dipropylamino)isoquinoline-7-carboxylic acid (104 mg): ESI MS m/z 273 [M + H]⁺.

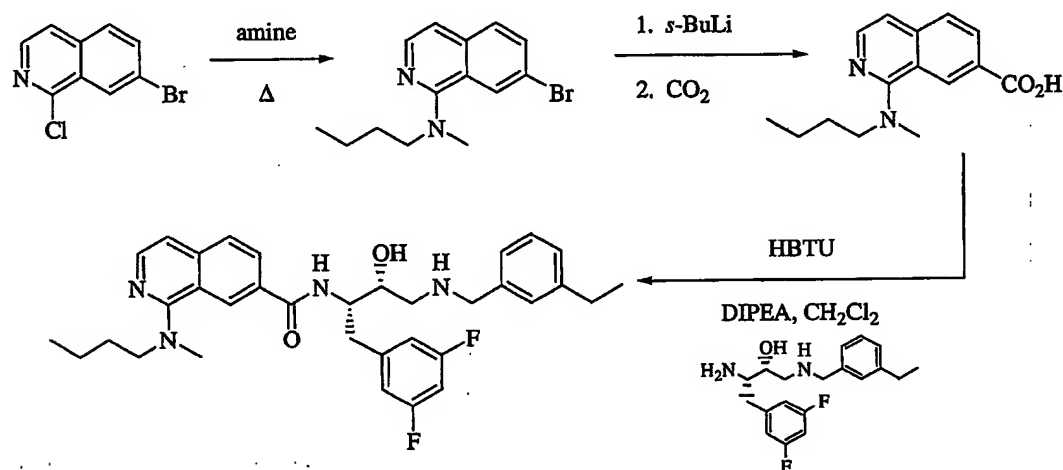
25 Step 5: To a stirred solution of 1-(dipropylamino)isoquinoline-7-carboxylic acid (103 mg, 0.38 mmol), (2R,3S)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (154 mg, 0.38 mmol), HOBt (77 mg, 0.57 mmol), and DIPEA (0.2 mL, 1.1 mmol) in methylene chloride
30 (4 mL) was added HATU (216 mg, 0.57 mmol). The reaction mixture was stirred overnight and then partitioned between methylene chloride and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and

concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gave N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(dipropylamino)isoquinoline-7-carboxamide

(70 mg): mp: 142-151 °C; APCI MS m/z 589 $[M + H]^+$

EXAMPLE SP-244

1-[butyl(methyl)amino]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-
[3-ethylbenzyl)amino]-2-hydroxypropyl)isoquinoline-7-carboxamide



Step 1: A solution of 7-bromo-1-chloroisoquinoline (750 mg, 3.09 mmol) in *N*-methylbutylamine (7.0 mL) was heated at 65 °C in a sealed tube for 18 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with chloroform and washed with saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown oil. Purification by flash column chromatography (silica, 3:1 hexanes/diethyl ether) provided 7-bromo-N-butyl-N-methylisoquinolin-1-amine (730 mg): ESI MS m/z 293 $[M + H]^+$.

Step 2: To a -60 °C solution of 7-bromo-N-butyl-N-methylisoquinolin-1-amine (230 mg, 0.78 mmol) in diethyl ether

was added *sec*-butyllithium (1.00 mL of a 1.3 M solution in cyclohexanes, 1.30 mmol). The solution was stirred at -60 °C for 20 min then excess dry ice (CO₂) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The aqueous phase was concentrated under reduced pressure to yield a yellow oil. Purification by flash column chromatography (silica, 50:30:15:5 ethyl acetate/chloroform/methanol/ammonium hydroxide) provided 1-[butyl(methyl)amino]isoquinoline-7-carboxylic acid (90 mg): ESI MS *m/z* 259 [M + H]⁺.

Step 3: To a solution of 1-[butyl(methyl)amino]isoquinoline-7-carboxylic acid (130 mg, 0.5 mmol) and *N,N*-diisopropylethylamine (525 µL, 3.0 mmol) in methylene chloride (6.25 mL) was added HBTU (190 mg, 0.5 mmol) and the reaction mixture was stirred for 0.5 h. (2*R*,3*S*)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (174 mg, 0.42 mmol) was added in one portion and the reaction mixture was stirred at room temperature 18 h. The reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1-5% methanol in chloroform) gave 1-[butyl(methyl)amino]-*N*-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide (101 mg): mp 120-121 °C; ESI MS *m/z* 575 [M + H]⁺

30 EXAMPLE SP-244

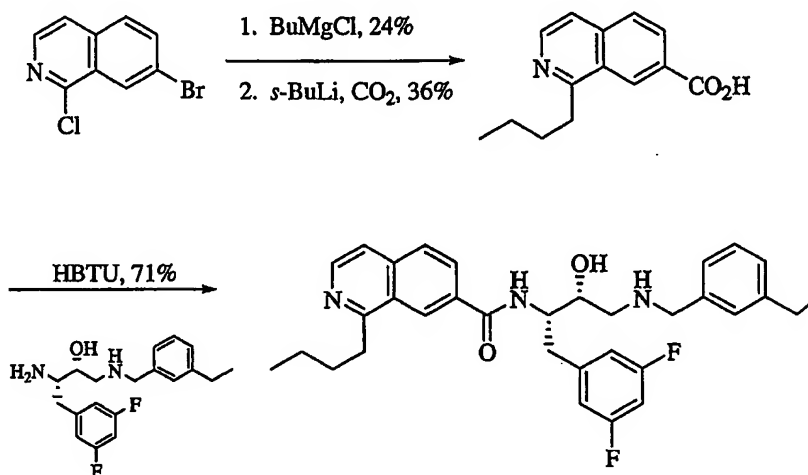
N-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[methyl(propyl)amino]isoquinoline-7-carboxamide

was prepared in a manner similar to that outlined above for 1-[butyl(methyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide. ESI MS m/z 561 $[M + H]^+$

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EXAMPLE SP-245

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide



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Step 1: To a refluxing solution of 7-bromo-1-chloroisoquinoline (4.85 g, 23.28 mmol) in diethyl ether (75 mL) was added butylmagnesium chloride (17.8 mL, 2.0 M ether, 35.6 mmol) and the reaction maintained at reflux for 2 h. The reaction mixture was cooled to room temperature, carefully diluted with an equal volume of ethyl acetate, washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a brown oil. Purification by flash column chromatography (silica, 1-10% ether/hexanes) gave the desired 7-bromo-1-butylisoquinoline (1.50 g): ESI MS m/z 264 $[M + H]^+$.

Step 2: To a -60 °C solution of 7-bromo-1-butylisoquinoline prepared in step 1 (940 mg, 3.55 mmol) in diethyl ether (15

mL) was added *sec*-butyl lithium (3.0 mL, 1.3 M cyclohexanes, 3.90 mmol) to yield a dark green solution. The reaction mixture was stirred at -60 °C for an additional 15 minutes at which time carbon dioxide gas was bubbled through the solution for 20 minutes with the aid of a gas dispersion tube. The resulting solution was then allowed to warm to room temperature and concentrated under reduced pressure to yield a pink solid. The residue was partitioned between ethyl acetate and water and then acidified to pH 7 with 1 N hydrochloric acid. The aqueous phase was extracted again with ethyl acetate and the combined organic phases were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield 1-butylisoquinoline-7-carboxylic acid (299 mg). ESI MS m/z 230 $[M + H]^+$.

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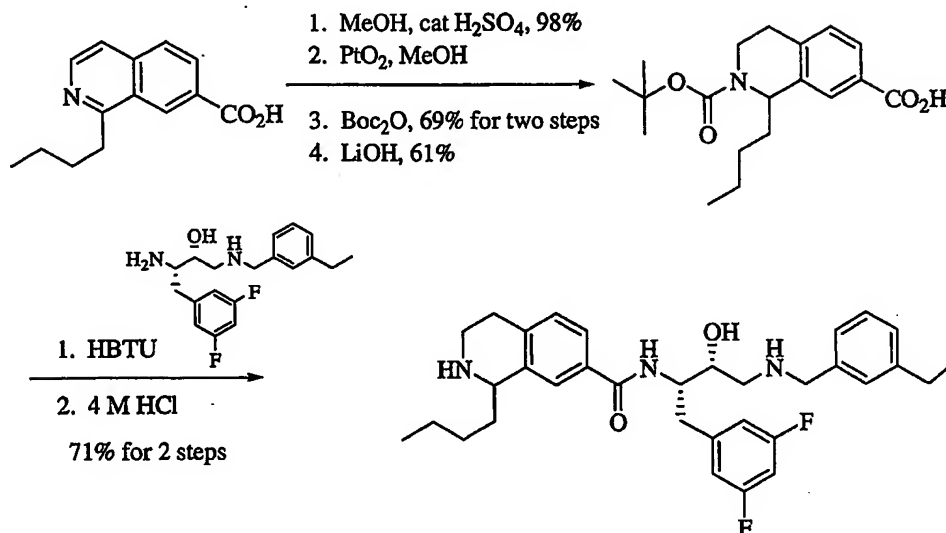
Step 3: To a solution of 1-butylisoquinoline-7-carboxylic acid (79 mg, 0.26 mmol) and *N,N*-diisopropylethylamine (150 μ L, 0.86 mmol) in methylene chloride (1.8 mL) was added HBTU (100 mg, 0.264 mmol) and the reaction mixture stirred for 0.5 h. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (107 mg, 0.264 mmol) in methylene chloride (1.8 mL) containing *N,N*-diisopropylethylamine (150 μ L, 0.86 mmol). The reaction mixture was then stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 93:7 chloroform/methanol) gave 1-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]isoquinoline-7-carboxamide (103 mg): mp 109-110 °C; ESI MS m/z 546 $[M + H]^+$.

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EXAMPLE SP-246

1-butyl-N-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

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Step 1: A solution of 1-butylisoquinoline-7-carboxylic acid (325 mg, 1.41 mmol) in methanol (25 mL) containing concentrated sulfuric acid (800 μ L) was refluxed overnight. The reaction mixture was then concentrated under reduced pressure, diluted with methylene chloride, washed with water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated to yield methyl 1-butylisoquinoline-7-carboxylate (350 mg): ESI MS m/z 244 [M + H]⁺;

Step 2: To a solution of methyl 1-butylisoquinoline-7-carboxylate prepared in step 1 (350 mg, 1.44 mmol) in methanol (6.0 mL) was added platinum(IV) oxide (35 mg) and the reaction mixture stirred under one atmosphere of hydrogen at room temperature overnight. The reaction mixture was concentrated under reduced pressure and redissolved in methylene chloride (15 mL). To this solution was added di-tert-butyl dicarbonate

(350 mg, 1.6 mmol), triethylamine (500 μ L, 3.11 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol), and the reaction mixture stirred at room temperature for 4 h. The reaction mixture was then diluted with methylene chloride, washed with
5 saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless oil. Purification by flash column chromatography (silica, 85:15 hexanes/ethyl acetate) yielded 2-tert-butyl 7-methyl
10 methyl 1-butyl-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (347 mg)l: ESI MS m/z 248 $[M + H]^+$.

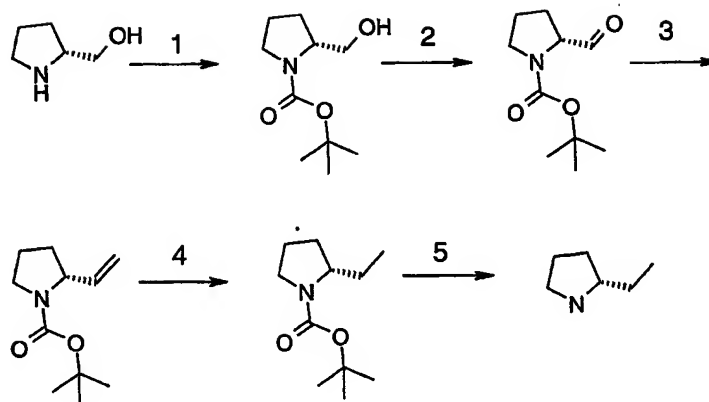
Step 3: To a solution of 2-tert-butyl 7-methyl 1-butyl-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate prepared in step 2
15 (347 mg, 1.0 mmol) in 2:1:1 dioxane/methanol/water (6.6 mL) was added lithium hydroxide monohydrate (125 mg, 3.0 mmol) and the reaction mixture stirred 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water.
20 The aqueous phase was acidified with 1 N hydrochloric acid to pH 1 and extracted several times with 3:1 chloroform/2-propanol. The combined organic phases were washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide
25 2-(tert-butoxycarbonyl)-1-butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (205 mg). ESI MS m/z 332 $[M - H]^-$.

Step 4: To a solution of 2-(tert-butoxycarbonyl)-1-butyl-
30 1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (205 mg, 0.61 mmol) and *N,N*-diisopropylethylamine (150 μ L, 0.86 mmol) in methylene chloride (4.0 mL) was added HBTU (233 mg, 0.61 mmol) and the reaction mixture stirred for 0.5 h. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol (250 mg, 0.61 mmol) in methylene chloride (4.0 mL) containing *N,N*-diisopropylethylamine (150 μ L, 0.86 mmol). The reaction mixture was then stirred at room temperature overnight. The reaction mixture was diluted with 5 methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 95:5 chloroform/methanol) gave the desired amide 10 product. The amide was then dissolved in dioxane (5.0 mL) to which was added hydrochloric acid (20 mL, 4.0 M dioxanes, 80 mmol) and the reaction mixture stirred overnight. The reaction mixture was then concentrated to dryness and purified by flash column chromatography (silica, 90:6:3:1 ethyl 15 acetate/chloroform/methanol/ammonium hydroxide) to yield a colorless oil. The oil was partitioned between 3:1 chloroform/2-propanol, washed with water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated to yield a white solid. The solid 20 was dried under high vacuum at 45 °C in the presence of P₂O₅ to yield 1-butyl-N-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (140 mg) characterized as a mixture of diastereomers: mp 121-124 °C; ESI MS *m/z* 550 [*M* + 25 H]⁺.

EXAMPLE SP-247

N-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[2*S*]-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride 30



Step 1: Di-*tert*-butyl-dicarbonate (10.8 g, 49 mmol) was added to an ice-cold solution of *R*-pyrrolidinemethanol (5.0 g, 49 mmol) and triethylamine (7.6 mL, 55 mmol) in 125 mL of CH₂Cl₂. The resultant solution was warmed to ambient temperature and stirred overnight. The reaction solution was then concentrated, diluted with EtOAc, washed 2X with 1 M KH₂PO₄ and 2X with brine, dried over Na₂SO₄, filtered, and concentrated to afford *tert*-butyl (2*R*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9.9 g).

Step 2: Oxalyl chloride (9.0 mL, 100 mmol) was added to a solution of DMSO (10.5 mL, 150 mmol) in 80 mL of CH₂Cl₂ at -78 °C, under a nitrogen atmosphere. The solution was stirred for 20 min at -78 °C, *tert*-butyl (2*R*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9.9 g, 49 mmol) was added, and the resultant solution stirred at -78 °C for 20 min. Triethylamine (28 mL, 200 mmol) was added to the reaction solution, the dry ice-acetone bath was removed, and the resultant solution was allowed to stir for two hours, slowly warming to ambient temperature. The reaction solution was quenched with brine, the phases were separated, and the organic phase was washed with 1 M KH₂PO₄ and saturated NaHCO₃. The organic solution was then dried over Na₂SO₄, filtered, and concentrated to an orange oil. This oil was then dissolved in heptane, filtered through

a plug of silica gel eluting with heptane, and the filtrate was concentrated to yield *tert*-butyl (2R)-2-formylpyrrolidine-1-carboxylate (7.87 g).

5 Step 3: *n*-Butyl lithium (1.6 M in hexanes) (27 mL, 43 mmol) was added to ice-cold hexamethyldisilazane (9.2 mL, 44 mmol) under a nitrogen atmosphere. The solution was stirred for 10 min and was then added to a suspension of methyl(triphenylphosphonium)bromide (15.5 g, 43 mmol) in 100
10 mL of THF at ambient temperature. After stirring for 1 h, the mixture was cooled to -78 °C and a solution of *tert*-butyl (2R)-2-formylpyrrolidine-1-carboxylate (7.9 g, 40 mmol) in 50 mL of THF was added. The cold bath was removed and the mixture stirred overnight at ambient temperature. The reaction
15 mixture was then quenched with saturated NH₄Cl, the phases were separated, and the organic phase was washed with saturated NH₄Cl, brine, dried over Na₂SO₄, filtered, and concentrated to give an orange oil. The oil was purified on a Biotage 40M column eluting with heptane to give *tert*-butyl (2R)-2-
20 vinylpyrrolidine-1-carboxylate (5.0 g).

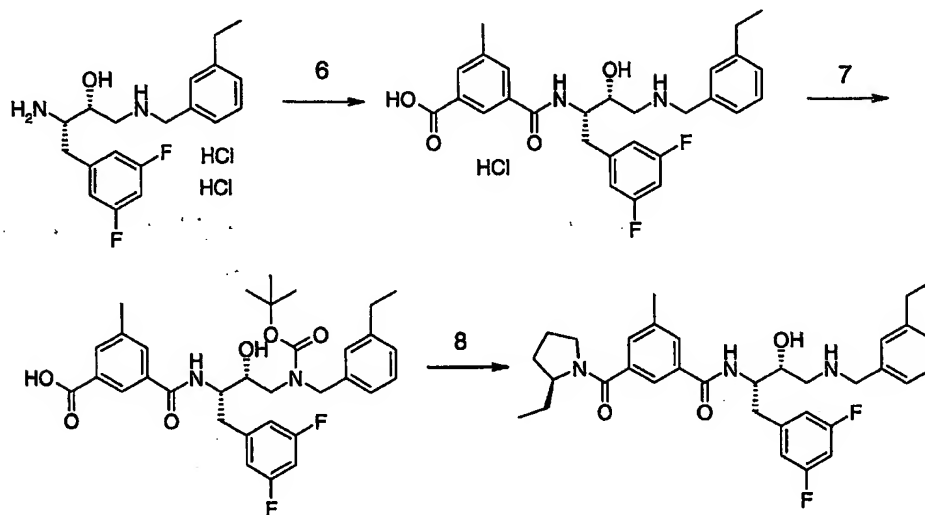
Step 4: To a suspension of palladium (II) hydroxide on activated carbon (20% by wt, 1.2 g) in 10 mL of ethanol was added *tert*-butyl (2R)-2-vinylpyrrolidine-1-carboxylate (2.0
25 g, 10 mmol) as a solution in 15 mL of ethanol and the mixture was placed under 12 psi of H₂ on a parr hydrogenator overnight. The resultant mixture was then filtered and concentrated to give *tert*-butyl (2S)-2-ethylpyrrolidine-1-carboxylate (1.5 g).

30

Step 5: To a solution of *tert*-butyl (2S)-2-ethylpyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) in 10 mL of dioxane was added 8 mL of 6N HCl and the resultant solution stirred overnight at ambient temperature. The reaction solution was then

concentrated, turned basic with solid KOH, and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated to give (2S)-2-ethylpyrrolidine hydrochloride (0.30 g).

5



Step 6: A solution of 3-(methoxycarbonyl)-5-methylbenzoic acid (0.48 g, 2.5 mmol), HATU (1.0 g, 2.6 mmol), and HOAT (0.37 g, 2.7 mmol) in 10 mL of dry DMF was stirred for an hour over ice, under a nitrogen atmosphere prior to the addition of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (1.0 g, 2.5 mmol) and DIPEA (1.8 mL, 10 mmol). The solution was stirred overnight at ambient temperature. The reaction solution was then quenched with 1 M HCl, diluted with EtOAc, and the phases were separated. The organic phase was washed with 1 M HCl, the combined acid washings were back-extracted with EtOAc, and the organic phases combined. The combined organic phases were then washed with saturated NaHCO₃, brine and dried over Na₂SO₄. The mixture was filtered and concentrated to give the coupled product as an orange oil. This oil was dissolved in 35 mL of MeOH and solid LiOH·H₂O (0.6 g, 14 mmol) was added with 2 mL of water. The mixture was stirred overnight at ambient

temperature. The solution was concentrated, diluted with water, neutralized with 1 M HCl, and concentrated. The resulting oily residue was purified on a Biotage 40S column eluting with 5% MeOH in CH₂Cl₂ to give a colorless oil. This
5 was dissolved in 10 mL of MeOH and 3 mL of 1 M HCl in ether was added. The solution was concentrated and the residue triturated with heptane to give 3-(((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-5-methylbenzoic
10 hydrochloride (0.65 g).

Step 7: To a solution of 3-(((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-5-methylbenzoic acid hydrochloride (0.50 g, 0.94 mmol) and di-
15 tert-butylidicarbonate (0.20 g, 0.92 mmol) in 10 mL of methanol and 10 mL of CH₂Cl₂ was added triethylamine (0.40 mL, 2.9 mmol). The solution was stirred for 2.5 hours at ambient temperature, at which time it was concentrated, partitioned between EtOAc and 1 M KH₂PO₄, and the phases were separated.
20 The organic phase was washed with M KH₂PO₄, dried over Na₂SO₄, filtered, concentrated, and triturated with heptane to give 3-(((1S,2R)-3-[(tert-butoxycarbonyl)(3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl)amino)carbonyl)-5-methylbenzoic acid (0.50 g).

25

Step 8: A solution of 3-(((1S,2R)-3-[(tert-butoxycarbonyl)(3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl)amino)carbonyl)-5-methylbenzoic acid (0.30 g, 0.50 mmol), HATU (0.19 g, 0.50 mmol) and HOAt (0.07 g, 0.51
30 mmol) in 5 mL of dry DMF under a nitrogen atmosphere was stirred for 15 minutes. A solution of (2S)-2-ethylpyrrolidine hydrochloride (0.05 g, 0.50 mmol) and DIPEA (0.35 mL, 2.0 mmol) in 5 mL of DMF was added. The solution was stirred overnight at ambient temperature. It was then quenched with 1

M HCl, diluted with EtOAc, and the phases were separated. The organic phase was washed with 1 M HCl, saturated NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to give an orange-brown oil. This oil was purified on a Biotage 40S column eluting
5 with 200 mL of CH₂Cl₂, then 3% MeOH in CH₂Cl₂. The yellow oil obtained was dissolved in 4 mL of CH₂Cl₂ and 4 mL of TFA was added. After stirring for two hours at ambient temperature the reaction solution was concentrated and the residue was purified by reverse phase prep hplc using a 1-inch Kromasil
10 c18 column to give the product as the formic acid salt. This was then converted to the HCl salt by the addition of 2 mL of 1 M HCl in ether. Upon concentration and trituration with heptane
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2S)-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride
15 was obtained (0.010 g). MS m/z 579.0 [M + H].

EXAMPLE SP-248

The following compounds,

- 20 3-[[2S)-2-butylpyrrolidin-1-yl]carbonyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methylbenzamide, MS m/z 606.4 [M + H];
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-5-[[2S)-2-propylpyrrolidin-1-yl]carbonyl}benzamide formic acid salt, MS
25 m/z 638.6 [M + H];
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2R)-2-(2-methoxyethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide, MS
30 m/z 608.6 [M + H]; and
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2S)-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide

hydrochloride; were prepared in a manner similar to that outlined above for EXAMPLE SP-247.

EXAMPLE SP-249

5 The following compounds;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl)-3-[[2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide
10 hydrochloride, MS m/z 608.3 [M + H];

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl)-3-[[2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide
hydrochloride, MS m/z 590.3 [M + H]; and

15 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[[2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide
hydrochloride, MS m/z 620.3 [M + H]; were also prepared using the methods disclosed herein.

20

EXAMPLE SP-250

Preparation of: N-[(1S,2R)-3-[[1-(3-bromophenyl)cyclopropyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide:

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Step 1: A stirred solution of N-((1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethyl)acetamide (4.96 g) and 1-(3-bromophenyl)cyclopropylamine (8.6 g) in 60 mL of *i*-PrOH was heated to 75 °C for 3 h. The cooled solution was evaporated
30 and the residue re-dissolved in ethyl acetate (200 mL). The organic layer was washed with 10 % aqueous HCl (25 mL x 2). The aqueous washings were extracted once with EtOAc (75 mL) and the combined organic layers washed with a saturated solution of NaCl (100 mL). The organic layers were then dried

over Na₂SO₄ and evaporated to yield a residue that was purified by column chromatography to give 5.0 g of tert-butyl (1S,2R)-3-{{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate.

5

Step 2: To a suspension of tert-butyl (1S,2R)-3-{{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (1.3 g) in 5.0 mL of dichloromethane was added 5.0 mL of trifluoroacetic acid at 23 °C. After stirring for 1 h, 10.0 mL of toluene was added and the solution evaporated. The resulting residue was re-dissolved in toluene and the solution evaporated. This procedure was repeated once more. After drying under high vacuum for 2 h, the residue was suspended in dichloromethane (10.0 mL) and triethylamine (0.5 g) and acetylimidazole (0.3 g) were added. The solution was stirred for 4 h and concentrated under reduced pressure. The residue was purified by column chromatography to yield 0.90 g of the title compound. ES+ found (M+H⁺): 455.

20

EXAMPLE SP-251

Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide:

25

To a solution of N-[(1S,2R)-3-{{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide (0.030 g) in DMF (0.75 mL) was added 3-methoxyphenylboronic acid (0.030 g), Cs₂CO₃ (0.085 g) and Pd(Ph₃P)₄. The mixture was heated for 12 h at 90 °C. The cooled solution was diluted with EtOAc (15 mL) and washed with brine (10 mL x 2). The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The

30

resulting residue was purified by column chromatography to give 0.010 g of the title compound. ES+ found (M+H⁺): 481.

EXAMPLE SP-251

- 5 N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3'-(hydroxymethyl)-1,1'-biphenyl-3-yl]cyclopropyl}amino)propyl]acetamide, was prepared by the method of N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-(3'-methoxy-1,1'-biphenyl-3-yl)10 cyclopropyl}amino)propyl]acetamide step 1, using 3-(hydroxymethyl)phenylboronic acid (0.036 g) to give 0.008 g of the title compound. ES+ found (M+H⁺): 481.

EXAMPLE SP-252A

- 15 N-[(1S,2R)-3-({1-(2'-acetyl-1,1'-biphenyl-3-yl)cyclopropyl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide was prepared by the method of N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl}amino)propyl]acetamide step 1,20 using 2-acetylphenylboronic acid (0.032 g) to give 0.012 g of the title compound. ES+ found (M+H⁺): 493.

EXAMPLE SP-252B

- N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(5-formylthien-2-yl)phenyl]cyclopropyl}amino)-2-hydroxypropyl]acetamide was25 prepared by the method of N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl}amino)propyl]acetamide step 1, using 5-formylthien-2-ylboronic acid (0.030 g) to give 0.005 g of the30 title compound. ES+ found (M+H⁺): 484.

EXAMPLES 2453A to 2453D

EXAMPLE SP-253A

N^1 -{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride;

5 EXAMPLE SP-253B

N^1 -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride;

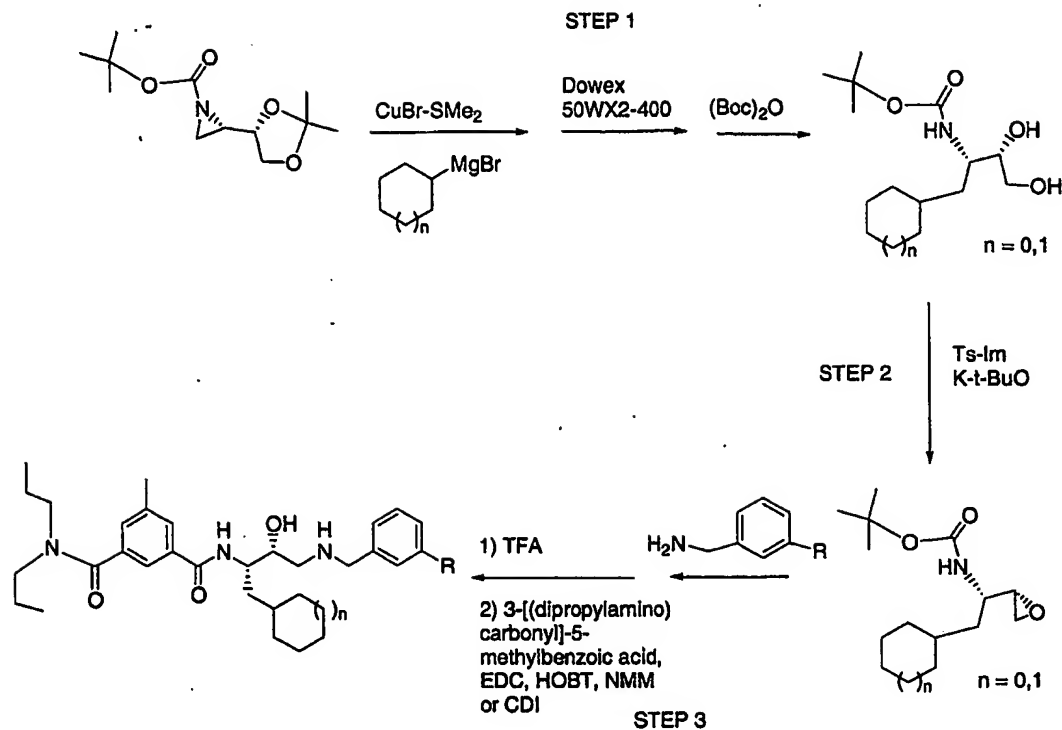
10 EXAMPLE SP-253C

N^1 -{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride;

15 EXAMPLE SP-253D

N^1 -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride;

20 EXAMPLE SP-254A



N^1 -{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride (EXAMPLE SP-254) and N^1 -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride (EXAMPLE SI-255)

Step 1: Cyclopentyl magnesium bromide (8 mL of 2M ethereal solution) was added to cuprous bromide/dimethylsulfide complex (0.33 g, 1.6 mmol) in 10 mL of dry THF cooled to -25°C under nitrogen. After 20 min, a solution of tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate (1.95 g, 8 mmol) in 4 mL of dry THF was introduced. The mixture was allowed to warm to ambient temperature overnight. It was quenched with saturated aqueous NH_4Cl and extracted with ethyl ether. The organic phase was washed with aqueous saturated NH_4Cl , 1 N NaHCO_3 , and brine. It was dried over anhydrous Na_2SO_4 and concentrated to 2.38 g of a solid. This material was dissolved in 70 mL of methanol, 12 g of Dowex 50WX2-400 was

added, and the mixture was refluxed for 2 h. The mixture was filtered, washing with methanol and dichloromethane. A clean receiver was attached, and the resin was washed with 100 mL of 1:1 concentrated NH_4OH : ethanol. The filtrate was concentrated to 1.16 g of tan crystals. The crystals were dissolved in 30 mL of dry THF, and 1.5 g (6.9 mmol) of di-*t*-butyldicarbonate was introduced. The mixture was stirred under nitrogen overnight. It was concentrated, extracted with ether and the ether was washed with several portions of water and brine. 10 Drying over Na_2SO_4 and concentration afforded 1.8 g (6.7 mmol, 84% from *tert*-butyl (2*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate) of *tert*-butyl (1*S*,2*S*)-1-[cyclopentylmethyl]-2,3-dihydroxypropylcarbamate: ^1H NMR (CDCl_3) δ 4.5 (d, 1 H, NH), 3.7 (m, 1 H), 3.6-3.49 (m, 2 H), 3.36 (m, 1 H), 3.26 (t, 1 H, OH), 2.76 (d, 1 H, OH), 1.45 (s, 9 H), 1.88-1.36 (m, 9 H), 1.17-1.08 (m, 2 H).

Step 2: Toluenesulfonyl imidazole (Ts-Im, 2.22 g, 10 mmol) was added to *tert*-butyl (1*S*,2*S*)-1-[cyclopentylmethyl]-2,3-dihydroxypropylcarbamate (1.8 g, 6.7 mmol) in 15 mL of dry THF under nitrogen, cooled in an ice bath. To this was added 13.4 mL (13.4 mmol) of a 1M solution of potassium-*t*-butoxide in THF over 8 min. After 5 min, the ice bath was removed and the orange mixture was stirred for 3 h. It was quenched with 1 N KH_2PO_4 and diluted with ether. The organic phase was washed with 1 N KH_2PO_4 , water, and brine. The solution was dried over Na_2SO_4 , concentrated, and chromatographed over silica gel, eluting with 5% dichloromethane, 15% ethyl acetate, and 80% heptane. Fraction 4 afforded 900 mg of a 2:1 mixture of *tert*-butyl (1*S*)-2-(cyclopentyl)-1-[(2*S*)-oxiran-2-yl]ethylcarbamate and a side product. Fraction 5 afforded 230 mg of *tert*-butyl (1*S*)-2-(cyclopentyl)-1-[(2*S*)-oxiran-2-yl]ethylcarbamate: ^1H NMR (CDCl_3) δ 4.56 (d, 1 H), 3.45 (m, 1 H), 2.85 (m, 1 H), 2.75 (m,

2 H), 1.91 (m, 1 H), 1.8 (m, 2 H), 1.6-1.4 (m, 6 H), 1.44 (s, 9 H), 1.13-1.07 (m, 2 H).

EXAMPLE SP-254B

5 N¹-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N³,N³-dipropylisophthalamide hydrochloride

Step 3: To tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (230 mg, 0.9 mmol) was added 260 mg (1.9 mmol) of m-ethylbenzylamine in 5 mL of isopropanol. The mixture was refluxed for 1.5 h under nitrogen, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue was partially purified by forming the HCl salt, triturating with pentane, and then neutralizing to the free base (290 mg, 0.74 mmol). To this was added 2 mL of trifluoroacetic acid (TFA) and 2 mL of dichloromethane, and the mixture was stirred under nitrogen for 30 min. It was concentrated to an oil which was dissolved in 2 mL of dry THF and neutralized with 0.2 mL of 4-methyl morpholine. To this mixture was added a solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (0.2 g, 0.76 mmol) and carbonyldiimidazole (CDI, 0.13 g, 0.8 mmol) in 3 mL of dry THF, which had been stirring together for 35 min. The reaction was stirred under nitrogen overnight. To the mixture was added 1 N KH₂PO₄ and ethyl acetate. The organic phase was washed with 1 N KH₂PO₄, 1 N NaHCO₃ (2X) and brine, dried over Na₂SO₄, and concentrated. Chromatography over silica gel, eluting with 6% methanol (containing 1% NH₄OH) in dichloromethane afforded 109 mg (0.19 mmol) of N¹-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-

ethylbenzyl)amino]-2-hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide hydrochloride (EXAMPLE SP-254) after formation of the salt with ethereal HCl: CI MS m/z 536 [M+H]⁺.

5 EXAMPLE SP-255

N¹-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide hydrochloride

- 10 Step 3: The fraction containing tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (ca. 2 mmol) and a side product, described in the above example, was reacted with m-bromobenzylamine (10 mmol) in 12 mL of isopropanol at reflux for 3 h. The solvent was removed and the
- 15 residue was dissolved in ethyl acetate. This was washed with several portions of 10% HCl, 1 N NaHCO₃, and brine, dried (Na₂SO₄), concentrated. Chromatography on silica gel, eluting with dichloromethane, then up to 2% of methanol (containing 1% NH₄OH) in dichloromethane afforded 523 mg (1.19 mmol, 60%
- 20 based on epoxide) of the oily addition product. This material (0.31 g, 0.7 mmol) was dissolved in 2 mL of dichloromethane, and 1 mL of TFA was added. After 1 h it was concentrated, dissolved in ethyl acetate, neutralized with 1 N NaHCO₃, washed with brine, and concentrated to the free base. To this was
- 25 added 4 mL of dry THF and a pre-mixed (for 2 h) solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (190 mg, 0.72 mmol) and CDI (120 mg, 0.74 mmol) in 3 mL of dry THF. After 2 days the reaction was quenched with 1 N KH₂PO₄ and dissolved in ethyl acetate.
- 30 The organic phase was washed with 1 N KH₂PO₄, 1 N NaHCO₃ (2X) and brine, dried over Na₂SO₄, and concentrated. Chromatography over silica gel, eluting with 5% methanol (containing 1% NH₄OH) in dichloromethane afforded 184 mg (0.29 mmol) of N¹-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-

hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide
hydrochloride EXAMPLE SP-255 as a white solid after formation
of the salt with ethereal HCl: CI MS m/z 586 [M+H]⁺.

- 5 N¹-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-
hydroxypropyl}-5-methyl-N³,N³-dipropylisophthalamide
hydrochloride (EXAMPLE SP-256) and N¹-[(1S,2R)-3-[(3-
bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-
methyl-N³,N³-dipropylisophthalamide hydrochloride (EXAMPLE SP-
10 257)

- Step 1: Cyclohexyl magnesium bromide was prepared by adding
cyclohexyl bromide (2.46 mL, 20 mmol) to magnesium turnings
(0.97 g, 40 mmol) in dry THF (20 mL) and refluxing for 1.5 h.
15 Following the procedures described in step 1 for the previous
EXAMPLE S-tert-butyl (1S,2S)-1-[cyclohexylmethy]-2,3-
dihydroxypropylcarbamate was obtained as 1.66 g (5.8 mmol, 70%
from tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-
yl]aziridine-1-carboxylate) of a slightly yellow oil which
20 solidified on standing: ¹H NMR (CDCl₃) δ 4.43 (d, 1 H, NH),
3.69 (m, 1 H), 3.59 (m, 2 H), 3.32 (m, 1 H), 3.24 (t, 1 H,
OH), 2.70 (d, 1 H, OH), 1.45 (s, 9 H), 1.8-1.13 (m, 11 H),
1.01 (m, 1 H), 0.87 (m, 1 H).

- 25 Step 2: tert-Butyl (1S,2S)-1-[cyclohexylmethy]-2,3-
dihydroxypropylcarbamate (1.6 g, 5.5 mmol) was reacted with
Ts-Im (1.5 g, 6.75 mmol) and potassium t-butoxide (11 mL of a
1 M solution in THF) in 20 mL of dry THF according to the
procedure described in step 2 for the preceding example.
30 Chromatography on silica gel, eluting with 5% dichloromethane
and 5%, increasing to 15% ethyl acetate in heptane afforded
456 mg 1.7 mmol, of tert-butyl (1S)-2-(cyclohexyl)-1-[(2S)-
oxiran-2-yl]ethylcarbamate: ¹H NMR (CDCl₃) δ 4.41 (m, 1 H),

3.55 (m, 1 H), 2.84 (m, 1 H), 2.75 (m, 2 H), 1.8-1.6 (m, 4 H),
1.45 (s, 9 H), 1.4-1.1 (m, 7 H), 0.98 (m, 1 H), 0.86 (m, 1H).

EXAMPLE SP-256

- 5 N¹-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N³,N³-dipropylisophthalamide hydrochloride

Step 3: tert-Butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (225 mg, 0.84 mmol) was refluxed with m-ethyl benzylamine (254 mg, 1.9 mmol) in 5 mL of isopropanol under nitrogen for 1.5 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous
15 phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The resulting oil (300 mg) was dissolved in 2 mL of dichloromethane and 2 mL of TFA and stirred for 30 min. It was concentrated, and by weight
20 determined to contain 4 eq. of TFA. This was dissolved in 2 mL of dry THF, and 0.4 mL (3.6 mmol) of 4-methyl morpholine was added. This was cooled to - 30°C, and a mixture of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (238 mg, 0.9 mmol) and CDI (165 mg, 1 mmol) in 3 mL of dry THF, which had
25 previously been stirred together for 1 h at room temperature, was added. The mixture was allowed to warm to ambient temperature. After 3 days the reaction was quenched with 1 N KH₂PO₄ and dissolved in ethyl acetate. The organic phase was washed with 1 N KH₂PO₄, 1 N NaHCO₃ (2X) and brine, dried over
30 Na₂SO₄, and concentrated. Chromatography over silica gel, eluting with 4% to 10% methanol (containing 1% NH₄OH) in dichloromethane afforded 124 mg (0.21 mmol) of N¹-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N³,N³-dipropylisophthalamide hydrochloride (EXAMPLE

SP-256) as a white solid after formation of the salt with ethereal HCl: CI MS m/z 550 $[M+H]^+$.

EXAMPLE SP-257

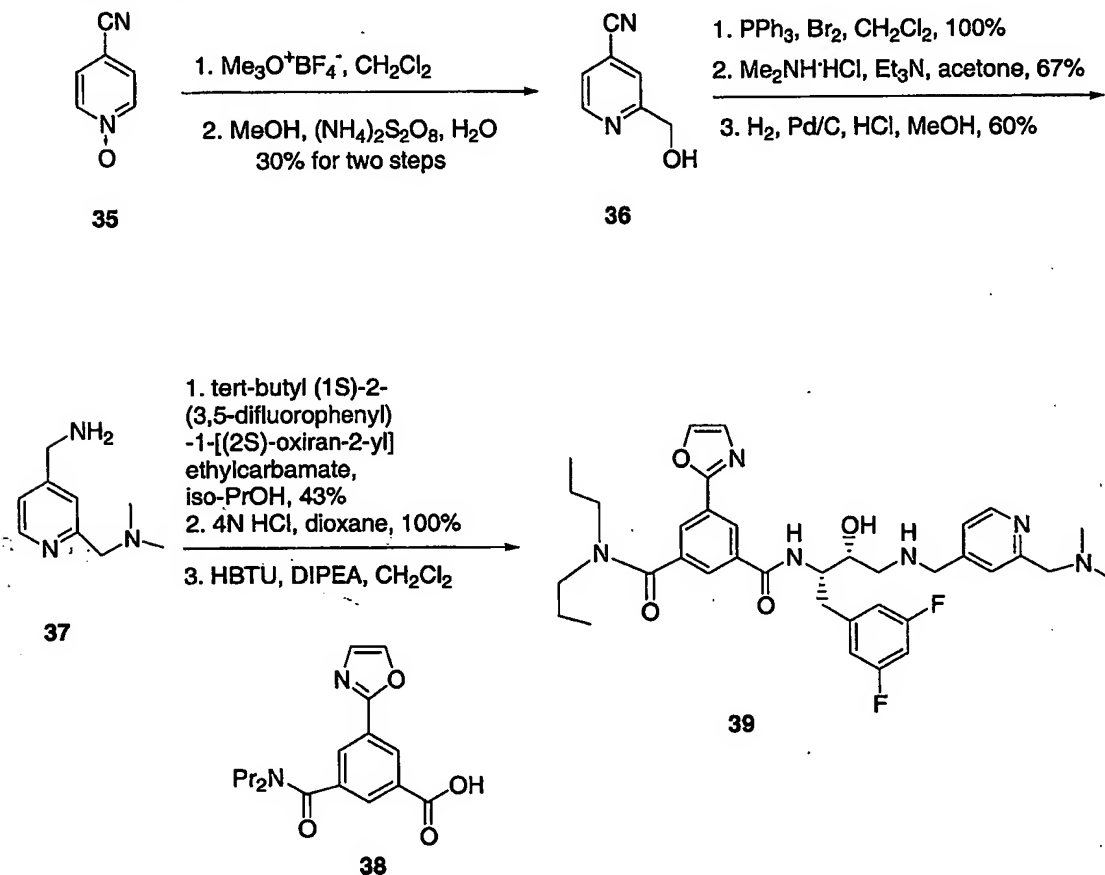
- 5 N^1 -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl- N^3,N^3 -dipropylisophthalamide hydrochloride

Step 3: tert-Butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (225 mg, 0.84 mmol) was refluxed with m-bromobenzylamine (380 mg, 2.0 mmol) in 7 mL of isopropanol under nitrogen for 2 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N $NaHCO_3$ and brine, dried over Na_2SO_4 , and concentrated. The resulting oil (356 mg) was dissolved in 3 mL of dichloromethane and 2 mL of TFA and stirred for 1.5 h. It was concentrated, and by weight determined to contain 3 eq. of TFA. To this was added 2 mL of dry dimethylformamide (DMF) and 0.35 mL (3.2 mmol) of 4-methylmorpholine. To this was added a pre-mixed solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (240 mg, 0.9 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 190 mg, 1 mmol), and 1-hydroxybenzotriazole hydrate (HOBT, 135 mg, 1 mmol) in 3 mL of dry DMF, which had been stirring together for 1.5 h. . After 3 days the reaction was quenched with 1 N KH_2PO_4 and dissolved in ethyl acetate. The organic phase was washed with 1 N KH_2PO_4 , 1 N $NaHCO_3$ (2X) and brine, dried over Na_2SO_4 , and concentrated. Chromatography over silica gel, eluting with 5% methanol (containing 1% NH_4OH) in dichloromethane afforded 208 mg (0.32 mmol) of N^1 -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl- N^3,N^3 -

dipropylisophthalamide hydrochloride (EXAMPLE SP-257) after formation of the salt with ethereal HCl: CI MS m/z 600 $[M+H]^+$.

EXAMPLE SP-258

- 5 Synthesis of $N^1-\{(1S,2R)-1-(3,5\text{-difluorobenzyl})-3-[(2-[(\text{dimethylamino})\text{methyl}] \text{pyridin-4-yl})\text{methyl})\text{amino}]-2\text{-hydroxypropyl}\}$
 dipropylisophthalamide $-5-(1,3\text{-oxazol-2-yl})-N^3,N^3-$



10

- Step 1: Trimethyloxonium tetrafluoroborate (2.46 g, 16.7 mmol) was added dropwise at room temperature to a solution of 4-cyanopyridine *N*-oxide (compound 35, above) (2.0 g, 16.7 mmol) in methylene chloride (260 mL) and the reaction mixture stirred at room temperature overnight. The reaction was concentrated under reduced pressure to give the desired 4-cyanopyridinium *N*-methoxy tetrafluoroborate: ^1H NMR (300 MHz,
- 15

DMSO- d_6) δ 9.80 (d, J = 6.0 Hz, 2H), 8.87 (d, J = 6.0 Hz, 2H), 4.48 (s, 3H).

Step 2: An aqueous solution of ammonium persulfate (8.3 mL, 8.3 mmol) was added to a refluxing solution of the N-methoxypyridinium salt prepared in step 1 was dissolved in methanol (200 mL). After stirring for 0.5 h, additional 1 M ammonium persulfate was added (4.2 mL, 4.2 mmol) and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was separated and washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (silica, 98:2 methylene chloride/methanol) gave 4-cyano-2-hydroxymethylpyridine (36) as a white solid (670 mg, 30%): ^1H NMR (300 MHz, CDCl_3) δ 8.75 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 0.5 Hz, 1H), 7.46 (dd, J = 5.3, 0.5 Hz, 1H), 4.85 (d, J = 5.3 Hz, 2H), 3.25 (t, J = 5.3 Hz, 1H).

Step 3: Bromine (1.07 mL, 20.8 mmol) was added slowly at 0 °C to a solution of triphenylphosphine (5.53 g, 21.1 mmol) in methylene chloride (97 mL). The solution was warmed to room temperature and a white precipitate was observed. 4-Cyano-2-hydroxymethylpyridine 36 (2.61 g, 19.5 mmol) in methylene chloride (20 mL) was added dropwise and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (silica, 99:1 methylene

chloride/methanol) gave 4-cyano-2-bromomethylpyridine (3.95 g), which was used immediately in the next step without further purification: ^1H NMR (300 MHz, CDCl_3) δ 8.76 (d, J = 5.0 Hz, 1H), 7.7 (s, 1H), 7.46 (dd, J = 5.0, 1.3 Hz, 1H), 4.58 (s, 2H).

Step 4: Dimethylamine hydrochloride (4.78 g, 58.6 mmol) was added to a solution of 4-cyano-2-bromomethylpyridine (3.95 g, 19.5 mmol) and triethylamine (13.58 mL, 97.7 mmol) in acetone (40 mL). The reaction mixture was stirred overnight at room temperature in a sealed tube. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was separated and washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 99:1 methylene chloride/methanol) gave the desired 4-cyano-2-(dimethylamino)methylpyridine (2.10 g): ^1H NMR (300 MHz, CDCl_3) δ 8.73 (d, J = 5.0 Hz, 1H), 7.71 (s, 1H), 7.41 (dd, J = 5.0, 1.2 Hz, 1H), 3.65 (s, 2H), 2.31 (s, 6H); ESI MS m/z 162 $[\text{M} + \text{H}]^+$.

Step 5: A mixture of 4-cyano-2-(dimethylamino)methylpyridine (800 mg, 4.97 mmol), palladium (80 mg, 10% Pd/C) and concentrated hydrochloric acid (3 mL) in methanol (30 mL) was shaken under 60 psi of hydrogen overnight. The reaction mixture was filtered through diatomaceous earth and the filter cake rinsed with water and methanol. The filtrate was concentrated under reduced pressure and the residue partitioned between water and methylene chloride. The aqueous layer was made alkaline with 1 N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate),

filtered, and concentrated under reduced pressure to give an orange oil. Purification by flash column chromatography (97:3 2-propanol/ammonium hydroxide) gave 4-aminomethyl-2-(dimethylamino) methylpyridine **37** (492 mg): ^1H NMR (500 Hz, CDCl_3) δ 8.50 (d, $J = 5.1$ Hz, 1H), 7.37 (s, 1H), 7.15 (d, $J = 5.1$ Hz, 1H), 3.91 (s, 2H), 3.58 (s, 2H), 2.30 (s, 6H); ESI MS m/z 166 $[\text{M} + \text{H}]^+$.

Step 6: A mixture of 4-aminomethyl-2-(dimethylamino) methylpyridine **37** (490 mg, 2.98 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl] ethylcarbamate (892 mg, 2.98 mmol) in 2-propanol (20 mL) was heated at reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (99:1 2-propanol/ammonium hydroxide) to give product (590 mg): ESI MS m/z 465 $[\text{M} + \text{H}]^+$.

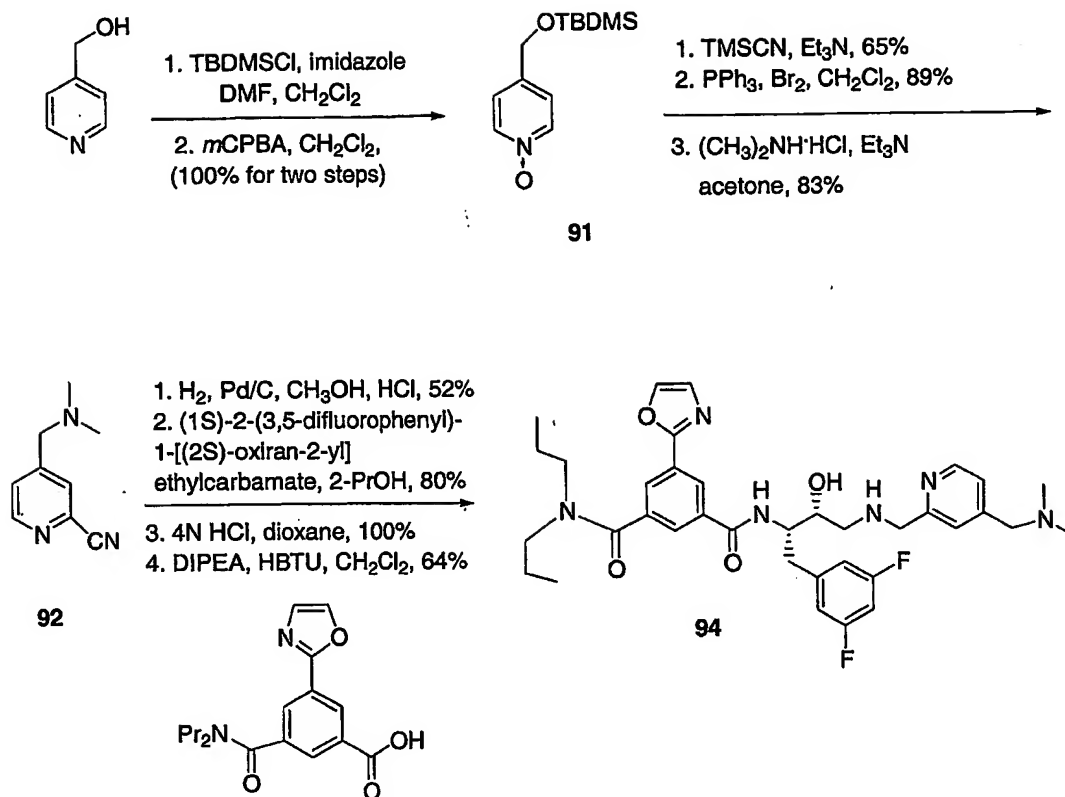
Step 7: Hydrogen chloride (6.3 mL of a 4 N solution in dioxane, 25 mmol) was added at room temperature to a solution of the yellow solid prepared in step 6 (590 mg, 1.26 mmol) in dioxane (6.3 mL) and the reaction mixture stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in methylene chloride containing *N,N*-diisopropylethylamine (3 mL). The organic phase was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the product (523 mg): ESI MS m/z 365 $[\text{M} + \text{H}]^+$.

Step 8: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **38** (120 mg, 0.38 mmol) in methylene chloride (3.8 mL) containing *N,N*-diisopropylethylamine (132 μL , 0.76 mmol) and HBTU (151 mg, 0.40 mmol) was stirred at

room temperature for 0.5 h. To the above solution was added a solution of the orange oil from step 7 (207 mg, 0.57 mmol) in methylene chloride (3.8 mL) containing N,N-diisopropylethylamine (132 μ L, 0.76 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 90:10 methylene chloride/methanol) gave N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-(dimethylamino)methyl]pyridin-4-yl)methyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide (178 mg): mp 63-66 °C; ESI MS m/z 663 [M + H]⁺.

EXAMPLE SP-259

Synthesis of N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(4-[(dimethylamino)methyl]pyridin-2-yl)methyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide, compound 94 in scheme 23, below



Synthesis of 2-cyano-4-(dimethylamino)methylpyridine (92)

- 5 Step 1: A mixture of 4-(hydroxymethyl)pyridine (17.4 g, 159 mmol), *t*-butyldimethylsilyl chloride (26.36 g, 174.88 mmol), and imidazole (13.31 g, 195.5 mmol) in *N,N*-dimethylformamide (200 mL) and methylene chloride (20 mL) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and then partitioned between water and a mixture of ethyl acetate and hexanes (1:1). The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (35.62 g): ¹H NMR (300 MHz, CDCl₃) δ 8.43 (d, *J* = 6 Hz, 2H), 7.13 (d, *J* = 6 Hz, 2H), 4.63 (s, 2H), 0.84 (s, 9H), 0.05 (s, 6H).
- 10
- 15

Step 2: To a stirred solution of the oil from step 1 (35.62 g, 159 mmol) in dry methylene chloride (470 mL) was added 3-

chloroperoxybenzoic acid (47.03 g, 172.57 mmol). The reaction mixture was stirred at room temperature overnight and then partitioned between water and methylene chloride. The organic layer was washed with saturated sodium sulfite, saturated sodium bicarbonate, 1 N sodium hydroxide, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 4-(*t*-butyldimethylsilyloxy)methylpyridine *N*-oxide **91** (37.8 g): ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, *J* = 6 Hz, 2H), 7.13 (d, *J* = 6 Hz, 2H), 4.59 (s, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

Step 3: A mixture of 4-(*t*-butyldimethylsilyloxy)methylpyridine *N*-oxide **91** (30 g, 125 mmol), triethylamine (40 mL), and trimethylsilylcyanide (44 mL, 360 mmol) was refluxed overnight. The black solution was cooled to room temperature and concentrated under reduced pressure to give a black gum. Purification by flash column chromatography (silica, 10:90 ethyl acetate/hexanes) gave an oil (20.3 g): ¹H NMR (300 MHz, CDCl₃) δ 8.50 (d, *J* = 5 Hz, 1H), 7.55 (s, 1H), 7.34 (d, *J* = 5 Hz, 1H), 4.66 (s, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

Step 4: Bromine (1.97 mL, 38.74 mmol) was added slowly at 0 °C to a solution of triphenylphosphine (10.29 g, 39.28 mmol) in methylene chloride (200 mL). The solution was warmed to room temperature and a white precipitate was observed. The brown oil from step 3 (9.0 g, 36.27 mmol) in methylene chloride (50 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a brown solid. Purification by flash column chromatography (silica, 17:83 ethyl acetate/hexanes) gave a white solid (6.20

g): ^1H NMR (300 MHz, CDCl_3) δ 8.71 (d, J = 3 Hz, 1H), 7.73 (s, 1H), 7.55 (dd, J = 6, 3 Hz, 1H), 4.42 (s, 2H).

Step 5: To a stirred solution of the solid from step 4 (9.1 g, 46.44 mmol) in acetone (90 mL) was added dimethylamine hydrochloride (11.36 g, 139.3 mmol) and trimethylamine (38.73 mL, 278.6 mmol). The reaction mixture was stirred overnight in a sealed bottle. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water, made alkaline with 1 N sodium hydroxide to pH 10 and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 2-cyano-4-(dimethylamino)methylpyridine **92** (6.2 g): ESI MS m/z 162 $[\text{M} + \text{H}]^+$.

EXAMPLE SP-260

N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(4-[(dimethylamino)methyl]pyridin-2-yl)methyl]amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3, N^3 -dipropylisophthalamide

Step 1: A mixture of 2-cyano-4-(dimethylamino)methylpyridine **92** (2.0 g, 12.4 mmol), 10% Pd/C (200 mg) and concentrated hydrochloric acid (8 mL) in methanol (180 mL) was shaken under 60 psi hydrogen overnight. The reaction mixture was filtered through diatomaceous earth and repeatedly washed with water and methanol. Methanol was removed under reduced pressure and the residue partitioned between water and methylene chloride. The aqueous layer was made alkaline with 1 N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (1.07 g): ^1H NMR (300 MHz, CDCl_3) δ 8.53 (d, J = 5 Hz, 1H),

7.25 (s, 1H), 7.13 (d, $J = 5$ Hz, 1H), 3.98 (s, 2H), 3.42 (s, 2H), 2.26 (s, 6H); ESI MS m/z 166 $[M + H]^+$.

Step 2: A mixture of the orange oil from step 1 (500 mg, 3.03 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (907 mg, 3.03 mmol) in 2-propanol (20 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 1:99 ammonium hydroxide/2-propanol) to give a solid (1.13 g): ESI MS m/z 465 $[M + H]^+$.

Step 3: The yellow solid from step 2 (400 mg, 0.86 mmol) was dissolved in dioxane (4.3 mL) and hydrogen chloride (4.3 mL, 4 M dioxane, 17.22 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and methylene chloride and *N,N*-diisopropylethylamine (3 mL) were added. The organic phase was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (365 mg): ESI MS m/z 365 $[M + H]^+$.

Step 4: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **93** (173.6 mg, 0.55 mmol) and *N,N*-diisopropyl ethylamine (191 μ L, 1.10 mmol) in methylene chloride (6.0 mL) was added HBTU (218.62 mg, 0.58 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution of the orange oil from step 3 (300 mg, 0.823 mmol) and *N,N*-diisopropylethylamine (191 μ L, 1.10 mmol) in methylene chloride (6.0 mL), and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, 0.5 N hydrochloric acid,

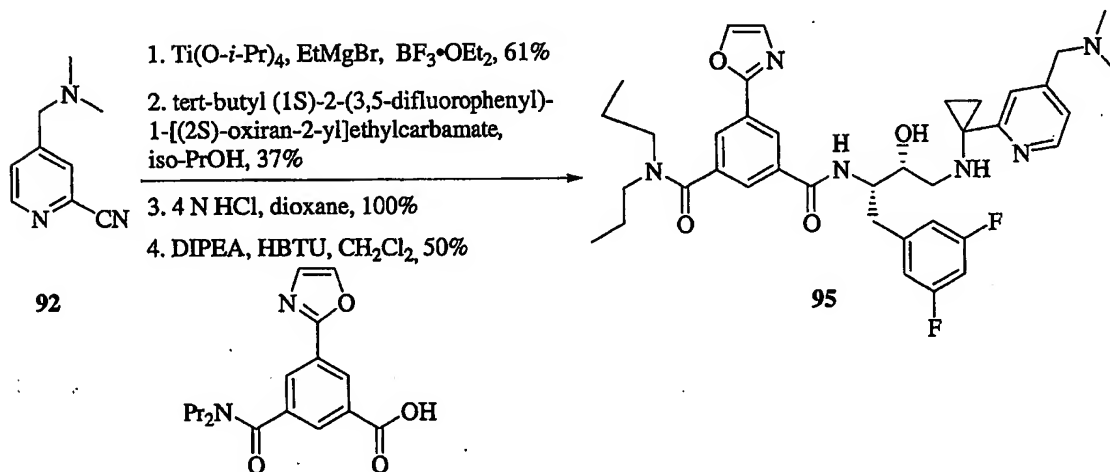
and saturated sodium chloride,. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 10:90 methanol/methylene chloride) gave N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(4-
 5 [(dimethylamino)methyl] pyridin-2-yl)methyl]amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3,N^3 -dipropylisophthalamide (**94**) (233 mg): mp 65-68 °C; ESI MS m/z 663 $[M + H]^+$

10

EXAMPLE SP-261

Synthesis of N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-{4-
 [(dimethylamino)methyl] pyridin-2-yl}cyclopropyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3,N^3 -dipropylisophthalamide

15



Step 1: To a solution of 2-cyano-4-(dimethylamino)methylpyridine **92** (prepared as in EXAMPLE SP-
 20 259) (500 mg, 3.10 mmol) in tetrahydrofuran (10 mL) was added titanium(IV) isopropoxide (1.01 mL, 3.41 mmol) and ethylmagnesium bromide (6.20 mL, 1 N THF, 6.20 mmol). After stirring for 0.5 h, boron trifluoride diethyl etherate (786 μ L, 6.20 mmol) was added in one portion. The reaction mixture
 25 was stirred for 1 h at room temperature and 1 N sodium hydroxide was added to adjust the mixture to pH 9-10. The

white solid generated was removed by filtration and the filtrate was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a yellow oil. Purification by flash column chromatography (silica, 1:99 to 3:97 ammonium hydroxide/2-propanol) gave an oil (360 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.42 (dd, $J = 6, 5$ Hz, 1H), 3.41 (s, 2H), 7.02 (dd, $J = 6, 5$ Hz, 1H), 3.98 (s, 2H), 3.42 (s, 2H), 2.25 (s, 6H), 2.08 (s, 2H), 1.31-1.27 (m, 2H), 1.15-1.11 (m, 2H); ESI MS m/z 192 $[\text{M} + \text{H}]^+$.

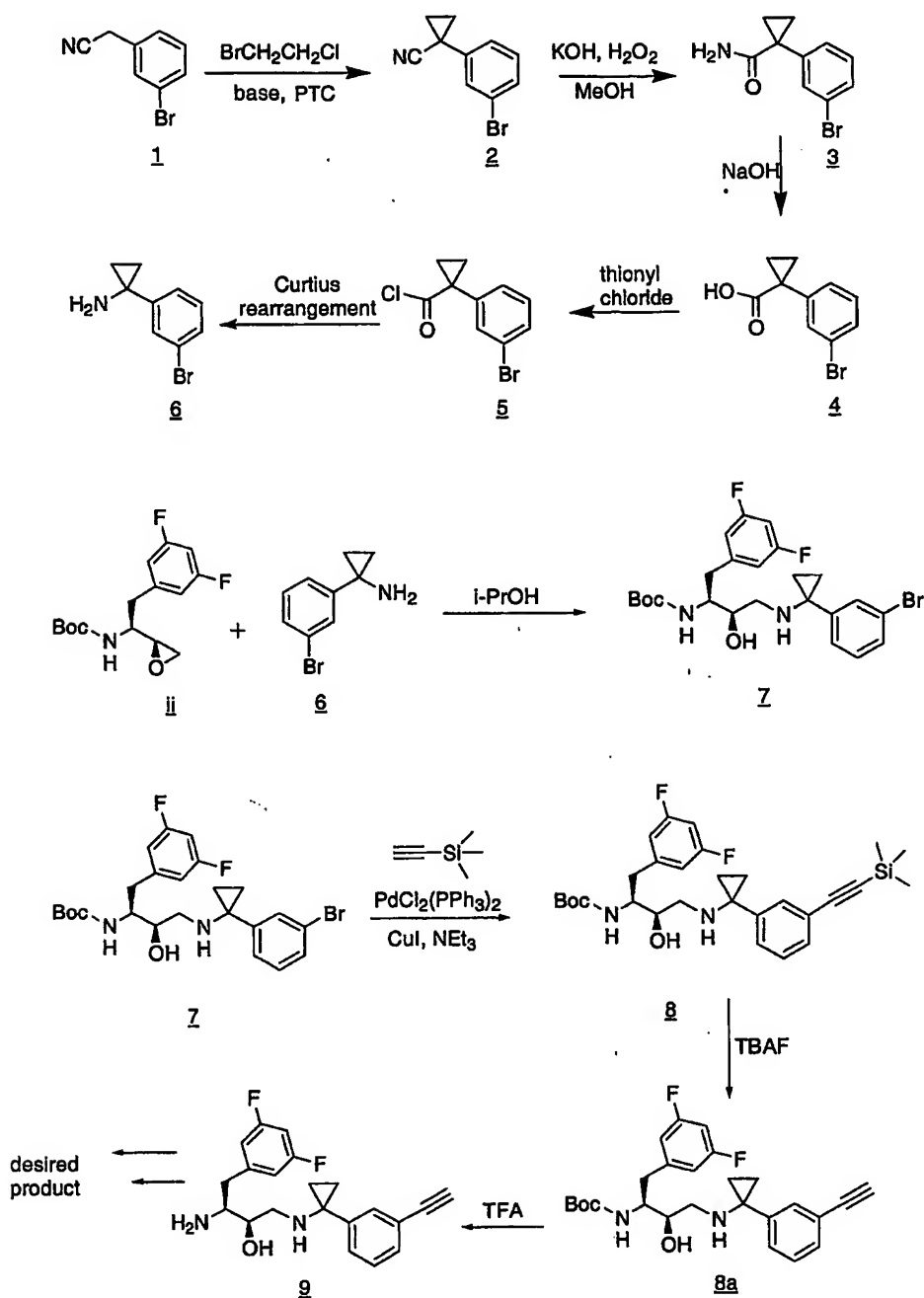
Step 2: A mixture of the oil from step 1 (350 mg, 1.83 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (496.8 mg, 1.66 mmol) in 2-propanol (13 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 1:99 ammonium hydroxide/2-propanol) to give a solid (300 mg): ESI MS m/z 491 $[\text{M} + \text{H}]^+$.

Step 3: To a stirred solution of the solid from step 2 (300 mg, 0.61 mmol) in dioxane (6.0 mL) was added hydrochloric acid (6.0 mL, 4 N dioxane, 24.40 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and methylene chloride and *N,N*-diisopropylethylamine (3 mL) were added. The organic layer was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (269 mg): ESI MS m/z 391 $[\text{M} + \text{H}]^+$.

Step 4: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **93** (prepared as in EXAMPLE S-

2364, step 5) (124.3 mg, 0.39 mmol) and *N,N*-diisopropyl ethylamine (139 μ L, 0.79 mmol) in methylene chloride (3.0 mL) was added HBTU (156.5 mg, 0.41 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution
5 of the orange oil from step 3 (269.6 mg, 0.823 mmol) and *N,N*-diisopropylethylamine (139 μ L, 0.79 mmol) in methylene chloride (3.0 mL), and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium
10 bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 10:90 methanol/methylene chloride) gave
15 N^1 -{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(1-{4-[(dimethylamino)methyl] pyridin-2-yl}cyclopropyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3,N^3 -dipropylisophthalamide
(**95**) (134 mg): mp 70-72 °C; ESI MS *m/z* 689 [M + H]⁺.

EXAMPLE SP-262



Preparation of bromo-cyclopropyl cyanide **2** (modification of procedure from Org. Prep. & Proc. Int., 1995, 27(3), 355)

- 5 A mixture of 1-bromo-2-chloroethane (BCE; 120 ml), 3-bromobenzyl cyanide (25 g) and benzyl-triethylammonium chloride (TEBAC, 1.1 g) was stirred at 40°C while base (50% NaOH , 120 g) was added dropwise over 20 min. Temperature has risen to $\sim 80^\circ\text{C}$ within first 15 min. Very vigorous mechanical

stirring was continued while temperature slowly dropped to 50°C (over the next 3 hr). The mixture was deep red at this stage. After 3 hr there was no starting material (TLC). The reaction mixture was cooled down to RT, water (100 ml) was added and stirred for 5 min. Organic layer was separated and aqueous was extracted with dichloromethane (3 x). Combined organic layers were washed with water and dil. aq. HCl. Solution was dried using MgSO₄, filtered and concentrated yielding deep yellow oil (126 g; still contains some BCE). Product was purified by a high vacuum fractionation using short-path set-up and single receiver. Collected fraction with bp 108-115°C / 0.1-0.05 mmHg as a heavy oily liquid 26.6 g (94%). After cooling to RT this liquid solidified.

15 Preparation of bromoamide 3

Bromocyanide 2 (5.9 g; 26.6 mmol) was dissolved in methanol (150 ml). To this solution while stirring KOH (25% aq soln., 0.68 ml) and hydrogen peroxide (30%, 35 ml) was added and the reaction mixture was heated at 55°C for 5 hr. At that time there was no starting material (TLC). Mixture was evaporated yielding solid residue (7.1 g; contains KOH).

Preparation of bromoacid 4

25

Crude bromoamide 3 from previous reaction was slurried in methanol (10 ml) and NaOH (10% aq, 150 ml) was added. Reaction mixture was refluxed 4.5 hr (TLC control). The mixture was cooled to RT, acidified with 15% HCl (to pH 2) and concentrated. Precipitated white solid was collected by filtration. Yield 6.8 g.

Preparation of acid chloride 5 (slight modification of procedure from Synlett 1999, 11, 1763)

Thionyl chloride (2.73 ml) and benzotriazole (4.47 g) were dissolved in dry dichloromethane (25 ml). Crude bromoacid 4 (6.8 g) was dissolved in dichloromethane (120 ml) and to this stirred solution the prepared above thionyl chloride solution (22.2 ml; 1.25 eq) was added portionwise over a few minutes. Before the addition was complete, benzotriazole hydrochloride started separating out as a white solid. The reaction mixture was stirred for additional 15 min and at the end the solids were filtered off. Filtrate was stirred with anhydrous MgSO_4 (2 g) to destroy an excess of reagent. The solids were filtered off and filtrate was evaporated and dried under high vacuum for 1 hr to give viscous amber oil. Yield 6.6 g.

15

Preparation of bromoamine 6

Crude acid chloride 5 was dissolved in dry acetone (40 ml), cooled to -10°C and treated with sodium azide (4 g in 15 ml of water). After stirring for 1 hr at -10°C a mixture was allowed to warm to 0°C and was poured into cold water (300 ml). Azide was extracted into smallest possible amount of toluene (ca. 40 ml). The toluene layer was washed with water and dried. Solids were filtered off and resulting solution was stirred and heated cautiously at 100°C for 1 hr. Conc. HCl (~25 ml) was added through condenser and mixture was refluxed for 15 min. On cooling white crystalline material precipitated and was filtered off. Filtrate was slightly concentrated, cooled down and additional portion of precipitate was collected. Combined solids were dried to give 4.1 g of bromo-cyclopropylamine 6 as hydrochloride salt.

30

Preparation of compound 7

Crude bromoamine hydrochloride **6** (2 g; 8 mmol) was dissolved in sat. aq Na_2CO_3 (20 ml) and extracted with dichloromethane (5 x 10 ml). Combined extracts were dried, evaporated and kept overnight under vacuum. Yield of
5 bromoamine **6** (1.68 g, 7.92 mmol). This amine was dissolved in isopropanol (20 ml) and epoxide (ii; 2.36 g, 7.92 mmol) was added. A mixture was stirred in a sealed tube at 80°C until starting epoxide was not detected by TLC (2-6 hr). Reaction mixture was cooled and solvent was evaporated to give, after
10 drying under vacuum, white solid (3.9 g, 82 % pure).

Preparation of compound **8**

Crude BOC bromide **7** (3.9 g; 7.0 mmol; 1 eq) was dissolved
15 in triethylamine (20 ml) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.196 g, 0.28 mmol; 0.04 eq) and CuI (0.068 g; 0.36 mmol; 0.05 eq) were added. Upon addition of CuI a reaction mixture turned yellow then changed color slowly to green. The reaction mixture was heated to reflux, at which point it turned orange-brown.
20 Trimethylsilyl acetylene (0.82 g, 1.2 ml, 8.2 mmol, 1.2 eq) was added via syringe. A black precipitate formed immediately. The reaction mixture was refluxed for 3 hr under nitrogen, then it was cooled to RT before partitioning between aq. sat. Na_2CO_3 and ethyl acetate. Organic layer was separated and
25 aqueous was extracted with ethyl acetate (3 x 25 ml). Combined extracts were washed with brine, dried and evaporated. The crude product was contaminated by acetylene derived from bromoamine **6**.

30 Preparation of BOC-acetylene **8a**

To a solution of crude silyl-protected acetylene **8** (from previous reaction) in THF (5 ml) the tetrabutylammonium fluoride (1M in THF, 8 ml) was added. Mixture was stirred for

1 hr at RT, solvent was evaporated, residue was dissolved in ether (30 ml), washed with brine, dried and concentrated. Crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane (2:3) mixture to give purified
 5 BOC-acetylene **8a** (1.54 g, 43% from **6**).

Preparation of **9**:

1-(3,5-difluorobenzyl)-3-[1-(3-ethynylphenyl)cyclopropylamino)]-2-hydroxypropyl amine
 10 dihydrochloride

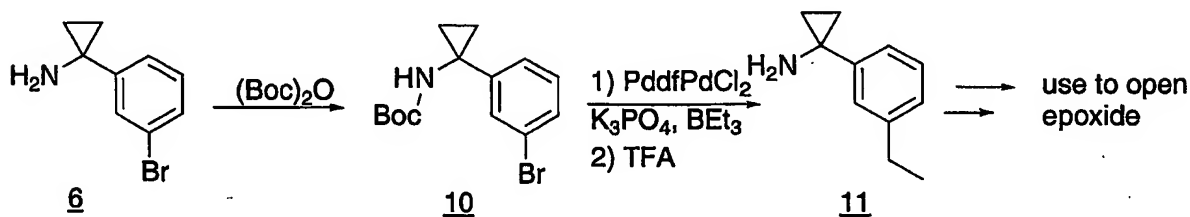
[1-(3,5-difluorobenzyl)-3-[1-(3-ethynylphenyl)cyclopropylamino)]-2-hydroxypropyl]-carbamic acid tert-butyl ester (2.34 g, 5.13 mmol) was treated with 4N HCl in dioxane (15.8 mL, 63.3. mmol). The resulting heterogeneous mixture was treated with methanol (10 mL) whereupon it became homogeneous over 30 min.. The volatiles were evaporated in vacuo. Dioxane (20 mL) was added and the mixture was evaporated in vacuo to produce a white solid (2.33 g, 106%).

20

EXAMPLE SP-263

Preparation of cyclopropyl m-ethylbenzylamine (**11**)

25



Preparation of **10**..

30

1-(3-Bromo-phenyl)-cyclopropylamine **6** (25 g, 112 mmol), triethylamine (21.7g, 2170 mmol) were mixed together in CH_2Cl_2 (300 mL). The solution was cooled to 0 °C and boc anhydride (25.07 g, 115 mmol) added in 4 equal portions at 15 minute

intervals. (Gas evolution noted after each addition). Mixture stirred for 30 minutes and then an additional 5 grams of boc anhydride was added to drive reaction to completion (GC/MS). Solution worked up with 1 N HCl (2X 100 mL), saturated aq. sodium bicarbonate (2 X 100 mL), and dried over sodium sulfate. Solvent was removed at reduced pressure and product was isolated by crystallization from cold hexanes (about 150 mL). Obtained 20.6 grams of white solid. Reduced volume of hexanes to about 75 ml and second crop was obtained (9.2 g)

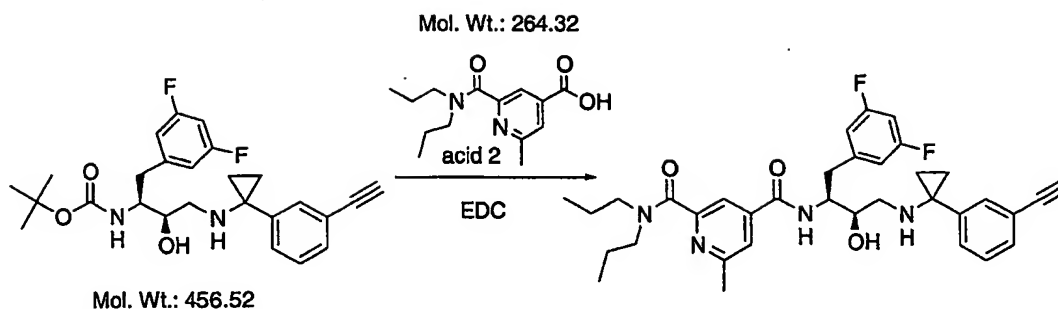
10

Preparation of 11.

The Boc-bromobenzyl amine 10 (26.8 g, 94.03 mmol), and Pd(dppf)Cl₂ (816 mg, 0.38 mmol, 0.004 eq) were mixed together in anhydrous THF (300 mL) and aqueous K₃PO₄ (100 mL of 2.0 M). To this red solution was added triethylborane (100 ml of 1.0 M in THF, 100 mmol). The solution turned black and was refluxed for 4 hours. GC/MS indicated the reaction was complete. The solution was poured into a separatory funnel and the aqueous layer separated. The organic layer was collected and solvent removed to a volume of 100 mL. Ethyl acetate/ hexanes (300 mL of 1:1) were added and the solution was extracted with 1N HCl (1X100 mL), sodium bicarbonate (2X 100 mL) and brine (1X100 mL). The solution was dried over sodium sulfate and vacuum filtered through a bed of silica gel (125 ml of silica). The solvent was removed at reduced pressure to afford 20.6 grams of 11 as light yellow oil.

EXAMPLE SP-264

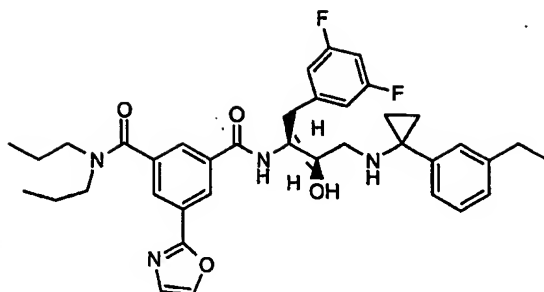
Preparation of 6-Methyl-pyridine-2,4-dicarboxylic acid 4-((1-(3,5-difluoro-benzyl)-3-[1-(3-ethynyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl)-amide) 2-dipropylamide



The Boc protected amine (prepared as in EXAMPLE SP-262) (0.912 g, 2 mM) was treated with 50% TFA in CH₂Cl₂ (1 hr, RT). Solvents were removed under reduced pressure to form an oil. Added toluene and evaporated; repeated stripping with toluene. After this operation and keeping residue under high vacuum for 1 hr off-white solid was obtained (free amine, most likely as a TFA salt). This amine was dissolved in CH₂Cl₂ (10 mL, slurry), added acid 2 (0.528 g; 2 mM), HOBt (0.297 g; 2.2 mM) and EDC (0.423 g; 2.2 mM). When EDC was added slurry rapidly became clear solution. At the end an excess of NEt₃ (2 mL) was added and a reaction mixture was stirred o/n at RT. The next day solvent was stripped and EtOAc solution was washed with aq. saturated solution of Na₂CO₃ (3x), brine, dried and concentrated. Initially purified by flash chromatography on Biotage (eluted with 20% hexane and 80% EtOAc). Final purification was done by HPLC. The TFA salt was converted into HCl mono salt by addition of 1.25M solution of HCl in MeOH (1.6 mL). Yield 0.971 g (76%).

EXAMPLE SP-265

N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide;



The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

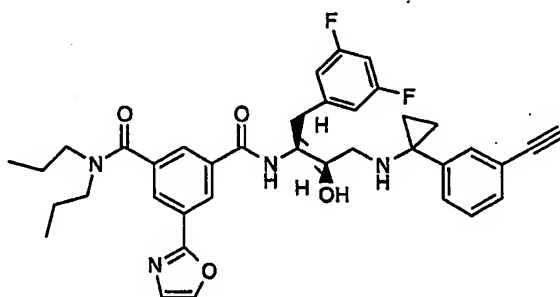
M+ 659.3.

5 Carbon NMR (CDCl₃): 11.00, 11.56, 11.78, 15.37, 20.80, 21.90, 28.71, 35.28, 44.45, 47.26, 49.97, 51.16, 53.75, 69.43, 77.12, 102.12, 112.02, 112.34, 126.23, 126.94, 127.29, 128.01, 128.68, 129.20, 129.51, 133.90, 134.70, 137.56, 139.59, 142.15, 145.53, 160.26, 161.43, 164.73, 166.98, 170.42.

10

EXAMPLE SP-266

N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide



15

The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

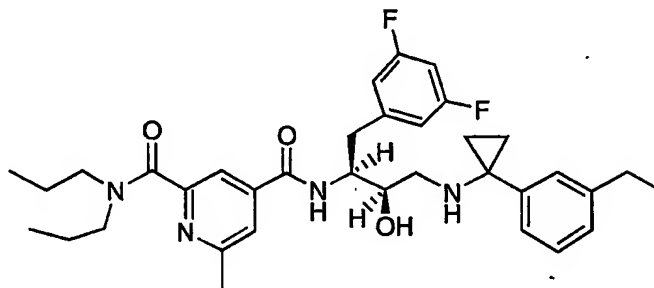
M+ 655.3.

Carbon NMR (CDCl₃): 11.01, 11.47, 11.58, 11.98, 20.82, 21.91,
20 35.22, 43.94, 47.28, 50.09, 51.17, 53.77, 69.49, 77.11, 78.63, 82.55, 102.17, 112.05, 123.22, 126.23, 126.82, 128.07, 128.76,

129.49, 130.68, 133.33, 134.50, 137.57, 139.61, 142.17,
160.23, 161.27, 164.56, 167.04, 170.44.

EXAMPLE SP-267

- 5 N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-
ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-6-methyl-N²,N²-
dipropylpyridine-2,4-dicarboxamide



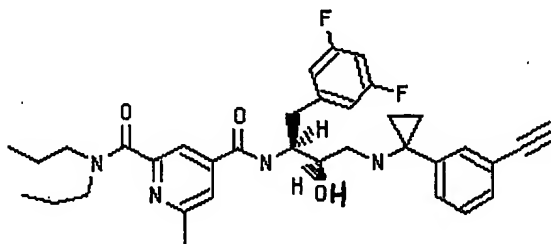
- The above identified compound is prepared essentially
10 using the procedure described in EXAMPLE SP-264.

M+ 607.3

- Carbon NMR (CDCl₃): 10.96, 11.06, 11.53, 12.09, 15.43, 20.73,
21.90, 23.96, 28.75, 33.93, 44.32, 47.82, 49.60, 50.90, 53.98,
68.65, 77.11, 101.98, 112.064, 112.39, 117.03, 122.12, 127.25,
15 129.23, 129.49, 134.06, 142.21, 145.61, 153.63, 158.94,
161.19, 161.36, 164.48, 164.65, 165.65, 169.06.

EXAMPLE SP-268

- N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-
20 ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-6-methyl-
N²,N²-dipropylpyridine-2,4-dicarboxamide



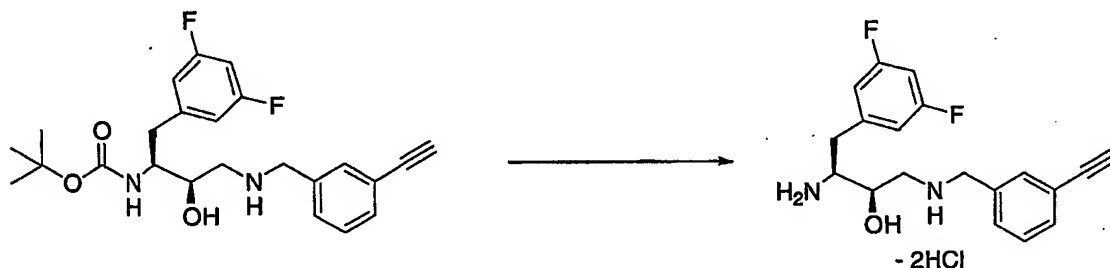
The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 603.3.

Carbon NMR (CDCl₃): 10.99, 11.58, 12.29, 20.75, 21.92, 24.03,
 5 33.98, 43.91, 47.91, 49.83, 50.96, 53.95, 68.74, 77.13, 78.72,
 82.57, 102.08, 112.08, 112.41, 117.63, 122.16, 123.32, 129.51,
 130.66, 133.37, 133.55, 134.63, 142.28, 153.56, 158.96,
 161.20, 161.37, 164.66, 165.80.

EXAMPLE SP-269

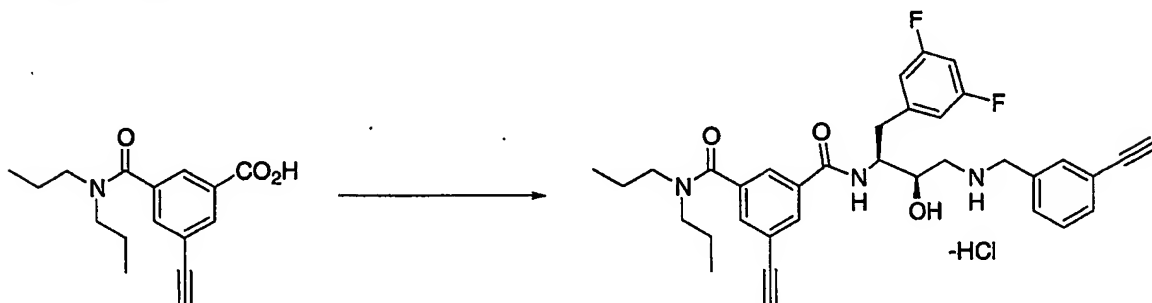
10 Preparation of 1-(3,5-difluorobenzyl)-3-(3-ethynylbenzylamino)-2-hydroxypropyl amine dihydrochloride



[1-(3,5-difluorobenzyl)-3-(3-ethynylbenzylamino)-2-hydroxypropyl]-carbamic acid tert-butyl ester (2.73 g, 6.33
 15 mmol) was treated with 4N HCl in dioxane (15.8 mL, 63.3 mmol). The mixture became homogeneous after 5 min and then deposited a precipitate. Diethyl ether (15 mL) was added to aid stirring and the mixture was stirred for 2 h. The volatiles were evaporated in vacuo. Dioxane (20 mL) was added
 20 and the mixture was evaporated in vacuo to produce a white solid (2.67 g, 104%).

EXAMPLE SP-270

N^1 -{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl- N^3,N^3 -dipropylisophthalamide



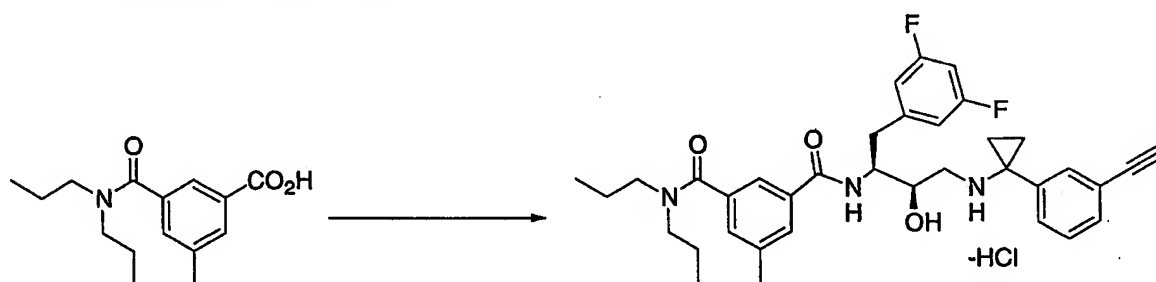
5 5-Ethynyl-*N,N*-dipropyl-*iso*-phthalamic acid (1.73 g, 6.32 mmol) was dissolved in anhydrous DMF (20 ml) under nitrogen. 1-Hydroxybenzotriazole (1.28 g, 9.48 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (1.70 g, 8.85 mmol) were added in succession. This mixture was stirred
 10 for 30 min at RT until homogeneous and then was added in one portion to a rapidly-stirred slurry of amine dihydrochloride (2.67, 6.32 mmol) and *N*-methylmorpholine (2.78 mL, 2.56 g, 25.3 mmol) in DMF (25mL). The resulting mixture was stirred for 2 h before diluting with saturated aq sodium bicarbonate
 15 (200 mL). The mixture was extracted with ethyl acetate (3 X 100 mL) and the combined organic extracts were washed with saturated aq sodium bicarbonate (100 mL), water (2 X 100 mL), and brine (100 mL), dried (sodium sulfate), filtered and evaporated *in vacuo* to give an oil (3.7 g). The product was
 20 purified using flash column chromatography on silica gel (Flash 65i cartridge, eluting with 1L 100% ethyl acetate, then 4L 95:5 ethyl acetate/methanol) to yield a pale yellow oil (2.74 g, 74%). LC-MS (*m/e*): 586 (*M*+1); 100% (254 nm). The ELN 152006 free base was dissolved in ethanol (25 mL) and treated
 25 with 4*N* HCl in dioxane (2.0 mL). The resulting mixture was evaporated *in vacuo* to remove volatiles, re-dissolved in 1:1 ethanol/water (25 mL) and evaporated *in vacuo*. The resulting solid was slurried in diethyl ether (50 mL), filtered and washed with diethyl ether to produce an off-white solid which

was vacuumed dried to constant weight (2 d) to yield the desired product (2.43 g).

Analysis: for $C_{35}H_{37}F_2N_3O_3 \cdot HCl$: calcd.: C, 67.57; H, 6.16; N, 6.75; Cl, 5.50; found: C, 67.21; H, 6.04; N, 6.55; Cl, 5.71.

EXAMPLE SP-271

Preparation of $N^1-((1S,2R)-1-(3,5\text{-difluorobenzyl})-3-[[1-(3\text{-ethynylphenyl})\text{cyclopropyl}]\text{amino}]-2\text{-hydroxypropyl})-5\text{-methyl-}$
 $N^3,N^3\text{-dipropylisophthalamide}$



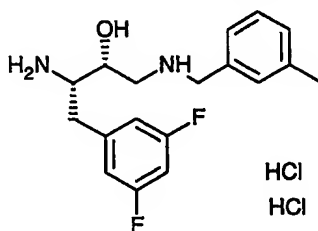
5-Methyl-N,N-dipropyl-iso-phthalamic acid (1.35 g, 5.13 mmol), was dissolved in anhydrous DMF (15 ml) under nitrogen.
 1-Hydroxybenzotriazole (1.04 g, 7.69 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.38 g, 7.18 mmol) were added in succession. This mixture was stirred for 30 min at RT until homogeneous and then was added in one portion to a rapidly-stirred slurry of amine dihydrochloride (2.23 g, 5.13 mmol) and N-methylmorpholine (2.25 mL, 2.07 g, 20.5 mmol) in DMF (20 mL). The resulting mixture was stirred for 3.5 h before diluting with saturated aq sodium bicarbonate (150 mL). The mixture was extracted with ethyl acetate (3 X 100 mL) and the combined organic extracts were washed with saturated aq sodium bicarbonate (100 mL), water (2 X 100 mL), and brine (100 mL), dried (sodium sulfate), filtered and evaporated in vacuo to give an oil (3.0 g). The product was purified using flash column chromatography on silica gel (Flash 65i cartridge, eluting with 2.8L 1:1 ethyl acetate/hexane, 2.5L 2:1 ethyl acetate/hexane, then 2L 100%

ethyl acetate) to yield a clear oil (2.34 g, 76%). LC-MS (m/e): 602 (M+1); 100% (254 nm). The ELN 152227 free base was dissolved in ethanol (25 mL) and treated with 4N HCl in dioxane (2.0 mL). The resulting mixture was evaporated in vacuo to remove volatiles, re-dissolved ethanol (25 mL) and evaporated in vacuo. The resulting solid was slurried in diethyl ether (50 mL) and filtered to produce a hygroscopic solid which was lyophilized to yield ELN 152227-3 (1.93 g).

Analysis: for $C_{36}H_{41}F_2N_3O_3 + HCl + 0.8 H_2O$: calcd.: C, 66.26; H, 6.73; N, 6.44; Cl, 5.43; found: C, 67.21; H 6.40; N, 6.42; Cl, 5.34.

EXAMPLE SP-272

Preparation of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride

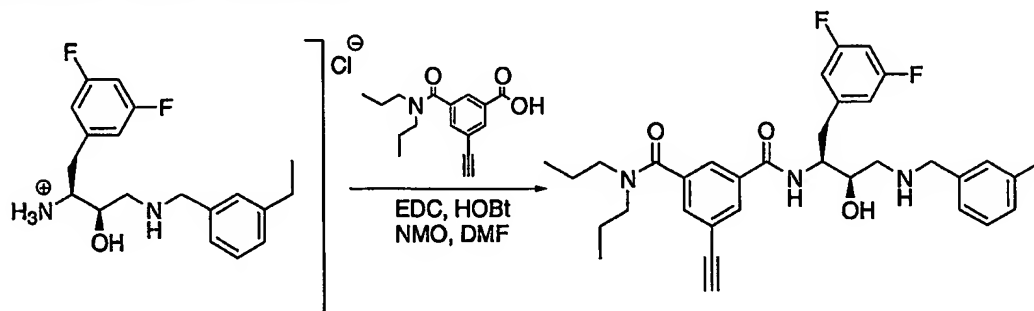


The slurry of [1-(3,5-difluorobenzyl)-3-(3-ethylbenzylamino)-2-hydroxypropyl]-carbamic acid tert-butyl ester (5.25 g, 0.012 m) in anhydrous dioxane (20 ml) was stirred (magnetic bar) at RT under nitrogen atmosphere in an 250 ml round-bottom flask, immersed in a cold water bath. The solution of hydrogen chloride in dioxane (4M, 32 ml) was added in one portion. The reaction mixture, initially homogenous, became a thick slurry within ca. 20 min. Mixture was stirred for 70 min, and was monitored by the TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate - methanol 95:5 mixture). Ethyl ether (100 ml) was added, precipitated product was filtered off and rinsed with ether (2 x 50 ml). The filter cake was air-dried for 1 hour then placed in an vacuum oven at

35 °C and the oven evacuated (5 torr). Product was dried to constant mass for 7 hours. Yield was 5.24 g. LC-MS (m/e): 335 (M+1); purity: 100% (254 nm).

5 EXAMPLE SP-273

N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N³,N³-dipropylisophthalamide



- 10 The 5-ethynyl-N,N-dipropyl-iso-phthalamic acid (1.64 g, 0.006m) was dissolved in anhydrous DMF (30 ml) in a round-bottom flask (50 ml) equipped with magnetic stirring bar. Flask was flushed with nitrogen and HOBT (1.23 g, 0.009m, 1.5 eq), followed by EDC (1.63 g, 0.0084m, 1.4 eq) were added.
- 15 This mixture was stirred for 45 min at RT and then was added in one portion to the stirred solution of amine hydrochloride (2.45 g, 0.006m) in anhydrous DMF (30 ml) and NMO (5.0 g, 0.05m, 8.5 eq). The resulted heterogeneous mixture was vigorously stirred under nitrogen at RT for 2 hr. During that
- 20 time all solids gradually dissolved, mixture remained however cloudy. Reaction progress was monitored by TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate-methanol 95:5 mixture). Product was isolated by diluting reaction mixture with sat. aq. sodium bicarbonate (250 ml) and extraction with
- 25 ethyl acetate (3 x 150 ml). Combined extracts were washed with brine and dried over magnesium sulfate. Solution was filtered and evaporated, yield of crude product was 4.6 g (yellow oil). Product was purified using flash column chromatography on silica gel (Flash 65i cartridge, applied in dichloromethane

solution and eluted with ethyl acetate-methanol 93:7 mixture). Fractions containing product were combined and evaporated to give pale yellow oil, 2.7 g. LC-MS (m/e): 590 (M+1); 100% (254 nm). Purified product was treated with ethanolic hydrogen chloride (1.05 eq), filtered and lyophilized. Yield of final hydrochloride salt was 2.4 g. LC-MS (m/e) 590 (M+1); purity: 100% (254 nm), 100% (280 nm).

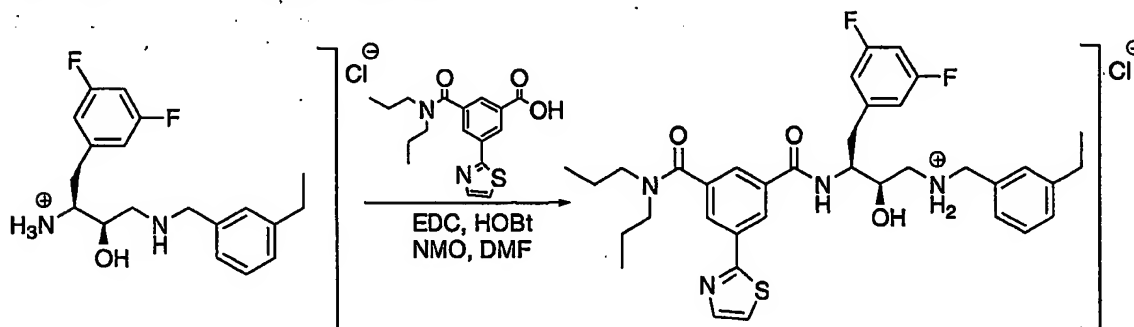
¹H-NMR (MeOH-d₄): δ 0.70 (t, 3H), 1.01 (t, 3H), 1.23 (t, 3H), 1.53 (m, 2H), 1.73 (m, 2H), 2.67 (q, 2H), 2.87 (m, 1H), 3.05-3.35 (m, 8H), 4.00 (s, 1H), 4.01 (m, 1H), 4.25 (m, 3H), 4.91 (s), 6.77 (m, 1H), 6.91 (d, 2H), 7.29-7.38 (m, 4H), 7.56 (d, 2H), 7.79 (s, 1H).

¹³C-NMR: (MeOH-d₄): 9.73, 10.17, 20.17, 21.33, 46.51-48.32, 49.27, 50.71, 54.04, 68.75, 79.79, 80.94, 101.17 (t), 111.56 (d), 123.26, 124.83, 127.00, 128.73, 129.23, 130.53, 130.95, 132.15, 134.29, 137.46, 142.69, 142.81, 145.17, 161.28 (d), 164.40 (d), 167.13, 170.28.

Analysis: for C₃₅H₄₂ClF₂N₃O₃ x 0.5 H₂O calcd.: C, 66.18; H, 6.82; N, 6.62; Cl, 5.58; found: C, 66.07; H 6.85; N, 6.79; Cl, 5.17.

EXAMPLE SP-274

Preparation of N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N³,N³-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide



The N,N-dipropyl-5-thiazol-2-yl-iso-phthalamic acid (1.99 g, 0.006m) was dissolved in anhydrous DMF (30 ml) in an round-

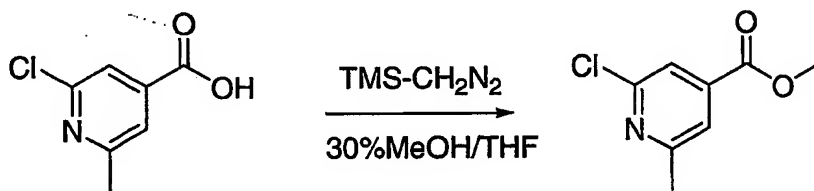
bottom flask (50 ml) equipped with magnetic stirring bar. Flask was flushed with nitrogen and HOBt (1.24 g, 0.009m, 1.5 eq), followed by EDC (1.63 g, 0.0084m, 1.4 eq) were added. This mixture was stirred for 45 min at RT and then was added
5 in one portion to the stirred solution of amine hydrochloride (2.45 g, 0.006m) in anhydrous DMF (30 ml) and NMO (5.0 g, 0.05m, 8.5 eq). The resulted heterogeneous mixture was vigorously stirred under nitrogen at RT for 2 hr. During that time all solids gradually dissolved, mixture remained however
10 slightly cloudy. Reaction progress was monitored by TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate-methanol 95:5 mixture). Product was isolated by diluting reaction mixture with sat. aq. sodium bicarbonate (250 ml) and extraction with ethyl acetate (3 x 150 ml). Combined extracts
15 were washed with brine and dried over magnesium sulfate. Solution was filtered and evaporated, yield of crude product was 4.2 g (pale yellow oil). Product was purified using flash column chromatography on silica gel (Flash 65i cartridge, applied in dichloromethane solution and eluted with ethyl
20 acetate-methanol 9:1 mixture). Fractions containing product were combined and evaporated to give pale yellow oil, 2.75 g. LC-MS (m/e): 649 (M+1); purity: 100% (254 nm). Purified product was treated with ethanolic hydrogen chloride (1.05 eq) and lyophilized (added ethanol to improve solubility before
25 filtration). Yield of final hydrochloride salt was 2.6 g. LC-MS (m/e): 649 (M+1); purity: 100% (254 nm).
¹H-NMR (MeOH-d₄): δ 0.74 (t, 3H), 1.04 (t, 3H), 1.20 (t, 3H), 1.58 (m, 2H), 1.77 (m, 2H), 2.64 (q, 2H), 2.92 (m, 1H), 3.10-3.55 (m, 9H), 4.04 (m, 1H), 4.26 (m, 2H), 4.90 (s), 6.77 (m,
30 1H), 6.96 (d, 2H), 7.23-7.38 (m, 4H), 7.68 (t, 1H), 7.73 (d, 1H), 7.96 (d, 1H), 8.11 (t, 1H), 8.28 (t, 1H).
¹³C-NMR: (MeOH-d₄): 9.76, 10.19, 14.75, 20.21, 21.39, 28.10, 35.38, 46.60-48.31, 50.75, 54.12, 68.78, 101.22 (t), 111.53 (d), 120.48, 125.65, 126.12, 126.97, 128.70, 129.218, 130.56,

133.96, 134.97, 138.00, 142.84, 143.53, 145.16, 161.31 (d),
164.52 (d), 165.96, 167.36, 170.47.

Analysis: for $C_{36}H_{43}ClF_2N_4O_3S \times 0.5 H_2O$ calcd.: C, 62.28; H,
6.39; N, 8.07; Cl, 5.11; found: C, 62.42; H 6.24; N, 8.03; Cl,
5.10.

EXAMPLE SP-275

2-Dipropylcarbamoyl-6-methyl-isonicotinic acid

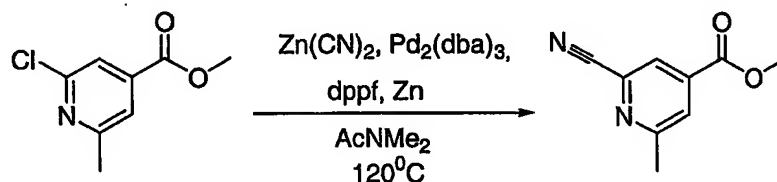


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Commercially available, 2-chloro-methylisotinic acid
(4.07g, 23.72 mmol) was dissolved in a 30%MeOH/ THF solution
(32 ml). (Trimethylsilyl)diazomethane (2.0 M solution in
15 hexanes) was added dropwise. Bubbling was observed and more
reagent was added until bubbling ceased (15mL). The reaction
mixture was allowed to stir overnight at room temp. Prior to
evaporation of solvent, glacial acetic acid was added to the
reaction flask dropwise in order to rid of excess amine.

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EXAMPLE SP-276



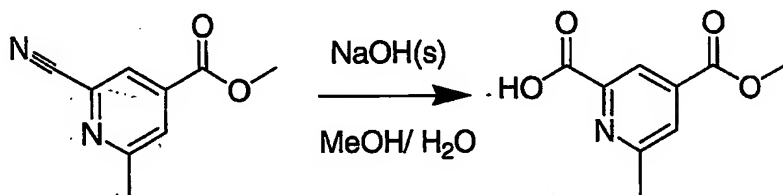
Reference: Fuqiang, J. and Confalone, N. Tet.
Lett., 41, 2000, 3271-3273

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Into a R.B flask equipped with a stir bar was added the
methylated intermediate, tri(dibenzlideneacetone)dipalladium

(0), 1,1-bis(diphenylphosphine), zinc metal dust and zinc cyanide. The flask was flushed with nitrogen gas for approx. 5 min. N,N-dimethylacetamide was added via syringe. The reaction mixture was refluxed in an oil bath set at 120°C with a condenser under nitrogen atmosphere. Stir vigorously. After 4 h, the reaction mixture was partitioned between ethyl acetate (50 ml) and 2N NH₄OH (50 ml) Repeat washing with 2N NH₄OH (2 x 50 ml) followed by brine (50 ml). Organic phases were collected and dried over Na₂SO₄, filtered and evaporated. Purification by column chromatography was performed with eluting solvent (80:20;Hex/EtOac).

EXAMPLE SP-277

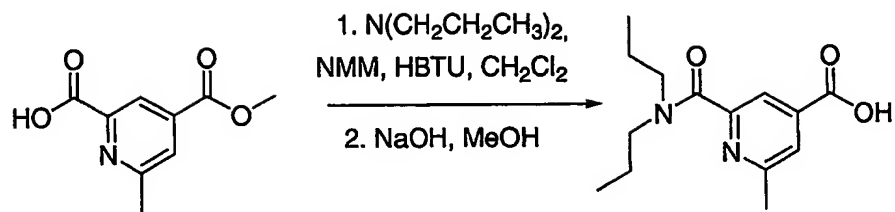


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Dissolve nitrile intermediate (0.206g, 1.170 mmol) in methanol (5 ml). Add sodium hydroxide (0.267g, 6.675 mmol) and continue to stir at room temp. After 90 min add water (5 ml) and continue to stir for an additional 90 min. Partition between chloroform and 2 N HCl (aq). Add NaCl(s) to aqueous phase in order to saturate. Continue extraction with isopropanol:chloroform (1:3). Collect organic phases, dry over NaSO₄, filter and evaporate.

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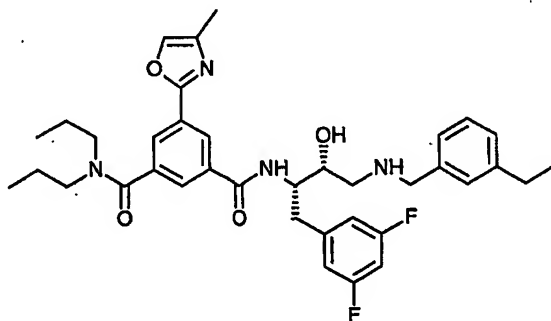
EXAMPLE SP-278



Anhydrous dichloromethane was added to the hydrolyzed intermediate (0.136, 0.697 mmol) followed by 4-methylmorpholine. The flask was placed on an ice bath to cool prior to addition of HBTU and dipropylamine. The mixture was allowed to warm to room temp. over night under nitrogen atmosphere. Partition reaction mixture between ethyl acetate (25 ml) and water (25 ml). Wash with water followed by sat. NaHCO_3 (2 x 25 ml). Organic phase was collected, dried over Na_2SO_4 , filtered and evaporated.

EXAMPLE SP-279

N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)- N^3 , N^3 -dipropylisophthalamide



Step 1: A stirred solution of methyl 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoate (200 mg, 0.65 mmol) chloroacetone (10 mL, 93 mmol) and potassium carbonate (90 mg, 0.65 mmol) was refluxed for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with 2 N sodium hydroxide (2 x 50 mL), and saturated sodium

chloride, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoate
5 (119 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.70 (d, $J = 1$ Hz, 1H), 8.20 (d, $J = 1$ Hz, 1H), 8.09 (d, $J = 1$ Hz, 1H), 7.48 (s, 1H), 3.96 (s, 3H), 3.46 (d, $J = 7$ Hz, 2H), 3.16 (t, $J = 7$ Hz, 2H), 2.26 (s, 3H), 1.71 (d, $J = 7$ Hz, 2H), 1.54 (d, $J = 7$ Hz, 2H), 1.00 (t, $J = 7$ Hz, 3H), 0.74 (t, $J = 7$ Hz, 3H); ESI MS m/z 345
10 $[\text{M} + \text{H}]^+$.

Step 2: A solution of methyl 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoate (118 mg, 0.34 mmol) in methanol (1 mL) and potassium hydroxide (1 mL of a 1.0 M
15 solution in water, 1 mmol) was stirred at room temperature for 45 min. The solvent was removed under reduced pressure, the residue was dissolved in water, extracted with ethyl acetate, the aqueous layer was acidified to pH 4 with 1 N hydrochloric acid, extracted with chloroform (3 x 100 mL), and the combined
20 organics were concentrated under reduced pressure to afford 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoic acid (110 mg): ^1H NMR (300 MHz, CD_3OD) δ 8.66 (d, $J = 1$ Hz, 1H), 8.17 (d, $J = 1$ Hz, 1H), 8.07 (d, $J = 1$ Hz, 1H), 7.75 (d, $J = 1$ Hz, 1H), 3.51 (t, $J = 7$ Hz, 2H), 3.25 (t, $J = 7$ Hz, 2H),
25 2.23 (s, 3H), 1.74 (d, $J = 7$ Hz, 2H), 1.60 (d, $J = 7$ Hz, 2H), 1.01 (t, $J = 7$ Hz, 3H), 0.76 (t, $J = 7$ Hz, 3H).

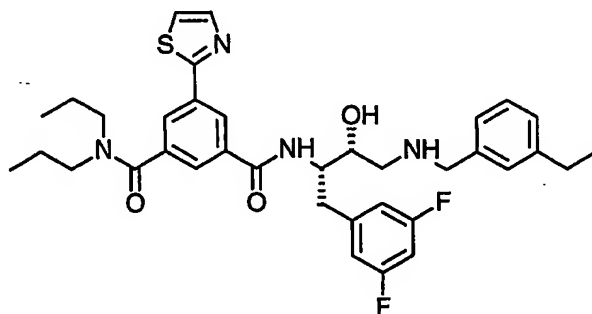
Step 3: A solution of 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoic acid (77.5 mg, 0.23 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-
30 ol dihydrochloride (96 mg, 0.23 mmol), HOBt (32 mg, 0.23 mmol), and *N*-methyldmorpholine (83 μL , 0.75 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (73 mg, 0.42 mmol) was added and the reaction mixture was stirred overnight. The

reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided

N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)- N^3,N^3 -dipropylisophthalamide (40 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.20 (br s, 1H, -NH), 8.17 (s, 1H), 8.05 (s, 1H), 7.52 (s, 1H), 7.38 (s, 1H), 7.24-7.08 (m, 5H), 7.02 (d, J = 8 Hz, 2H), 6.61 (t, J = 8 Hz, 1H), 4.27 (br s, 1H), 3.93 (d, J = 4 Hz, 1H), 3.85 (s, 2H), 3.54 (br s, 2H), 3.43 (br s, 2H), 2.84 (d, J = 5 Hz, 2H), 2.63 (q, J = 8 Hz, 2H), 2.18 (s, 3H), 1.74 (t, J = 5 Hz, 2H), 1.41 (d, J = 7 Hz, 2H), 1.22 (t, J = 8 Hz, 3H), 1.03 (t, J = 7 Hz, 3H), 0.64 (t, J = 7 Hz, 3H); ESI MS m/z 647 $[\text{M} + \text{H}]^+$

EXAMPLE SP-280

N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^3,N^3 -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide



Step 1: To a -78°C solution of thiazole (1.2 g) in THF (25 mL) was added n-butyl lithium (1.6 M in hexanes, 10 mL). The mixture was stirred for 30 min and then allowed to warm to 0°C

in an ice/water bath. Zinc chloride (1M in ethyl ether, 40 mL) was added and the mixture was stirred for 1 h, at which time methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (5.1 g) in THF (20 mL) was added, followed by Pd(PPh₃)₄ (palladium tetrakis triphenylphosphine) (0.68 g). The mixture was then heated at 80 °C for 2 h, at which time it was allowed to cool and partitioned between ethyl acetate and water. The organic layers were washed with brine, dried (magnesium sulfate), and concentrated. The residue was chromatographed on silica gel using ethyl acetate/heptane (50/50) to give 4.5 g of methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate.

Step 2: Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate (4.5 g) was dissolved in THF (20 mL), methanol (20 mL), and water (20 mL). Lithium hydroxide monohydrate (1.1 g) was added and the mixture was stirred at room temperature for 1.5 h, at which time the organic solvents were removed under reduced pressure. Some ethyl acetate and water were added and the pH was adjusted to about 0 with aq. HCl. The mixture was extracted with ethyl acetate and the organic layers were washed with brine, dried (magnesium sulfate), and concentrated to give 3.8 g of 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid

Step 3: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid (156 mg, 0.47 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (191 mg, 0.47 mmol), HOBt (64 mg, 0.47 mmol), and N-methylmorpholine (200 µL, 1.5 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (145 mg, 0.84 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate

(25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided

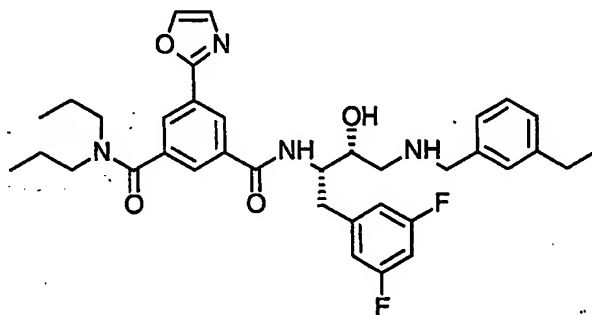
5 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^3 , N^3 -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide (33 mg): 1H NMR (500 MHz, $CDCl_3$) δ 8.40 (br s, 1H, -NH), 8.15 (br s, 1H), 7.94 (br s, 1H), 7.80 (d, J = 3 Hz, 1H), 7.51 (br s, 1H), 7.34 (d, J = 3 Hz, 1H), 7.27-7.24 (m, 1H), 7.21-7.18 (m, 2H), 7.11-7.10 (m, 1H), 7.00 (br s, 1H), 6.62-6.58 (m, 1H), 4.23 (d, J = 5 Hz, 1H), 3.91-3.85 (m, 3H), 3.57 (br s, 2H), 3.31 (br s, 2H), 3.05 (d, J = 5 Hz, 4H), 2.83 (d, J = 6 Hz, 2H), 2.64 (q, J = 8 Hz, 2H), 1.75 (br s, 2H), 1.44 (t, J = 7 Hz, 2H), 1.22 (t, J = 8 Hz, 3H) 1.04 (t, J = 7 Hz, 3H), 0.65 (t, J = 7 Hz, 3H); ESI MS m/z

15 649 $[M + H]^+$;

EXAMPLE SP-281

N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3 , N^3 -dipropylisophthalamide

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Step 1. To an ice-cold, stirred solution of 3-amino-5-(methoxycarbonyl)benzoic acid (5.19 g, 26.59 mmol) in a 2 N

25 hydrochloric acid (156 mL) was added a solution of sodium nitrite (1.84 g, 26.67 mmol) in water (10.8 mL). This mixture was then added dropwise to an ice-cold, stirred solution of potassium iodide (8.84 g, 53.25 mmol) in water (26.2 mL).

After stirring for 35 min, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium thiosulfate, and saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50:50:2 hexanes/ethyl acetate/acetic acid) afforded 3-iodo-5-(methoxycarbonyl)benzoic acid (4.48 g): ^1H NMR (500 MHz, DMSO- d_6): δ 13.49 (br s, 1H), 8.45-8.38 (m, 3H), 3.83 (s, 3H); ESI-MS (m/z): 305 [M + H] $^+$.

Step 2: To a mixture of 3-iodo-5-(methoxycarbonyl)benzoic acid (65.8 g, 0.215 mol), triethylamine (52.2 g, 0.516 mol), and dipropylamine (23.9 g, 0.237 mol) in methylene chloride (950 mL) was added 2-chloro-1-methylpyridinium iodide (65.9 g, 0.258 mol). The reaction mixture was stirred at room temperature for 15 h and then concentrated under reduced pressure. Purification by silica gel plug (3:1 hexanes/ethyl acetate) provided methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (66.8 g): ^1NMR (300 MHz, CDCl $_3$) δ 8.39 (s, 1H), 7.98 (s, 1H), 7.88 (s, 1H), 3.93 (s, 3H), 3.45 (m, 2H), 3.14 (m, 2H), 1.69 (m, 2H), 1.54 (m, 2H), 0.98 (m, 3H), 0.77 (m, 3H).

Step 3: A stirred solution of 2-triethylstannyloxazole (Chem. Mater. 1994, 6, 1023) (1.5 g, 5.5 mmol) and methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (1.8 g, 4.6 mmol) in dimethylformamide (12 mL) was degassed under reduced pressure for 15 min and purged with argon. Palladium(0) tetrakis(triphenylphosphine) (158 mg, 0.14 mmol) was added and the reaction mixture was degassed under reduced pressure for 15 min and then purged with argon. The reaction mixture was heated at reflux for 2 d, cooled to room temperature, diluted with ethyl acetate, washed with water (3 x 50 mL), dried

- (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (423 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.73 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 7.76 (s, 1H), 7.28 (s, 1H), 3.97 (s, 3H), 3.49 (br s, 2H), 3.18 (br s, 2H), 1.72 (d, $J = 7$ Hz, 2H), 1.55 (d, $J = 7$ Hz, 2H), 1.00 (t, $J = 7$ Hz, 3H), 0.75 (t, $J = 7$ Hz, 3H).
- 10 Step 4: A solution of methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (315 mg, 0.95 mmol) in methanol (3 mL) and potassium hydroxide (3 mL of a 1.0 M solution in water, 3 mmol) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, the residue
- 15 was dissolved in water, and extracted with ethyl acetate. The aqueous layer was acidified to pH 3 with 1 M hydrochloric acid, extracted with chloroform (3 x 100 mL), and the combined organic layers were concentrated under reduced pressure to afford 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic
- 20 acid (265 mg): ^1H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.08 (s, 2H), 8.05 (s, 1H), 7.34 (s, 1H), 3.52 (t, $J = 8$ Hz, 2H), 3.26 (t, $J = 8$ Hz, 2H), 1.75 (q, $J = 8$ Hz, 2H), 1.59 (q, $J = 8$ Hz, 2H), 1.02 (t, $J = 8$ Hz, 3H), 0.74 (t, $J = 8$ Hz, 3H).
- 25 Step 5: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (133 mg, 0.42 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (171 mg, 0.42 mmol), HOBt (57 mg, 0.42 mmol), and *N*-methylmorpholine (148 μL , 1.3 mmol) was stirred in
- 30 dimethylformamide (2 mL) for 15 min. EDC (130 mg, 0.75 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 M hydrochloric acid (25 mL), saturated sodium bicarbonate

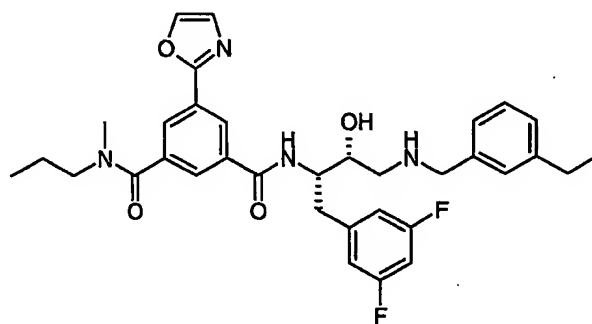
(25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided

5 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3,N^3 -dipropylisophthalamide (62 mg): mp 65-67 °C; 1H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 8.15 (s, 2H), 7.69 (s, 1H), 7.60 (s, 1H), 7.25 (t, J = 8 Hz, 1H), 7.19-7.17 (m, 3H), 7.10 (d, J = 8 Hz, 1H), 6.96 (d, J = 8 Hz, 2H), 6.60 (t, J = 8 Hz, 1H), 4.27
10 (d, J = 8 Hz, 1H), 3.88-3.80 (m, 3H), 3.53 (br s, 2H), 3.44 (br s, 2H), 3.09-3.01 (m, 4H), 2.85-2.82 (m, 2H), 2.62 (t, J = 8 Hz, 2H), 1.74 (br s, 2H), 1.45 (br s, 2H), 1.21 (t, J = 8 Hz, 3H), 1.03 (t, J = 7 Hz, 3H), 0.66 (t, J = 7 Hz, 3H); APCI MS m/z 633 $[M + H]^+$

15

EXAMPLE SP-281

N^1 -{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^3 -methyl-5-(1,3-oxazol-2-yl)- N^3 -
20 propylisophthalamide



To 3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (350 mg, 1.2 mmol) in DMF (5 mL) is added diisopropylethylamine (835 μ L, 4.8 mmol), HATU (554 mg, 1.5
25 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (488 mg, 1.2 mmol). The reaction is stirred for 16 h at room temperature. The reaction is

partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure.

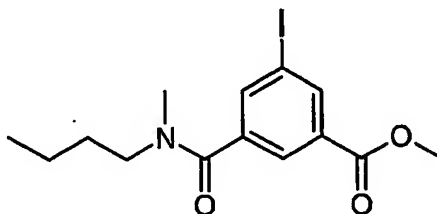
- 5 Purification by flash column chromatography (silica, 9% methanol/chloroform) gives the title compound. ESI MS m/z 605.3 $[M + H]^+$.

EXAMPLE SP-282

10

Step 1

Methyl 3-([butyl(methyl)amino]carbonyl)-5-iodobenzoate

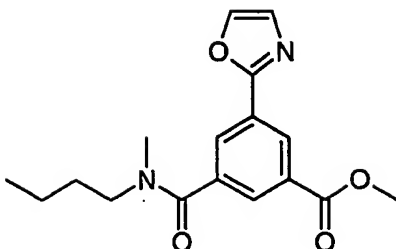


- 15 3-Iodo-5-(methoxycarbonyl)benzoic acid (1 g, 3.3 mmol) is dissolved in DMF (10 mL), and diisopropylethylamine (1.7 mL, 9.8 mmol), HATU (1.5 g, 3.9 mmol), and *N*-methylbutylamine (581 μ L, 4.9 mmol) are added. The reaction stirred at room temperature 2 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 40% ethyl acetate/hexane) provides the title compound. ESI MS m/z 376.1 $[M + H]^+$.

25

Step 2

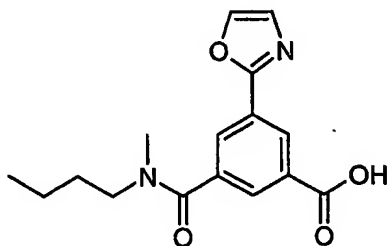
Methyl 3-([butyl(methyl)amino]carbonyl)-5-(1,3-oxazol-2-yl)benzoate



To a -70 °C stirred solution of oxazole (167 mg, 2.4 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 1.7 mL, 2.7 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 7.3 mL, 7.3 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-([butyl(methyl)amino]carbonyl)-5-iodobenzoate (864 mg, 2.3 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (112 mg, 0.10 mmol). The reaction mixture is heated at reflux for 1.5 h. The reaction mixture is cooled, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound. ESI MS *m/z* 317.1 [M + H]⁺.

Step 3

3-([Butyl(methyl)amino]carbonyl)-5-(1,3-oxazol-2-yl)benzoic acid



To methyl 3-([butyl(methyl)amino]carbonyl)-5-(1,3-oxazol-2-yl)benzoate (660 mg, 2.1 mmol) in tetrahydrofuran/methanol/water (1:1:1, 9 mL) is added lithium hydroxide monohydrate (175 mg, 4.2 mmol), and the reaction is

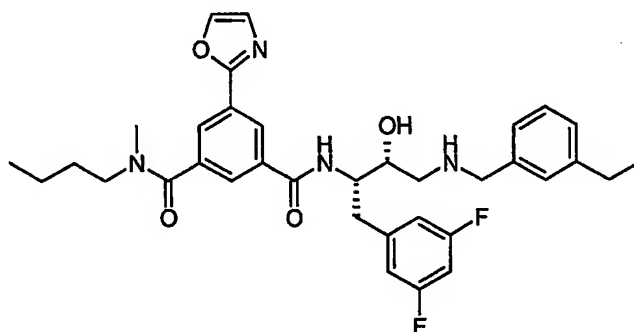
stirred at room temperature 16 h. The solution is diluted in chloroform and washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS

5 m/z 301.1 $[M - H]^-$.

Step 4

N^1 -butyl- N^3 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^1 -methyl-5-(1,3-oxazol-2-yl)isophthalamide

10



3-[(Butyl(methyl)amino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (237 mg, 0.78 mmol) is dissolved in DMF (5 mL), and diisopropylethylamine (546 μ L, 3.1 mmol), HATU (358 mg, 0.94 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (319 mg, 0.78 mmol) are added. The reaction stirred at room temperature 5 h. The reaction mixture is diluted with chloroform, washed with water, 1N hydrochloric acid (aq), saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS m/z 619.3 $[M + H]^+$.

15

20

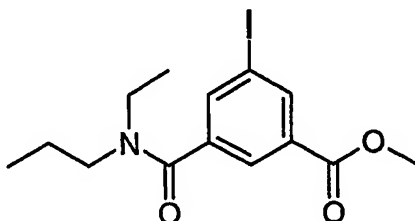
25

EXAMPLE SP-283

N^1 -{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^3 -ethyl-5-(1,3-oxazol-2-yl)- N^3 -propylisophthalamide

Step 1

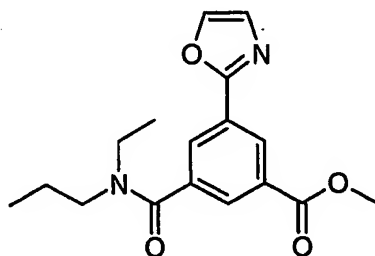
5 Methyl 3-{[ethyl(propyl)amino]carbonyl}-5-iodobenzoate



3-Iodo-5-(methoxycarbonyl)benzoic acid (1 g, 3.3 mmol) is dissolved in DMF (10 mL), and diisopropylethylamine (1.7 mL, 9.8 mmol), HATU (1.5 g, 3.9 mmol), and *N*-ethylpropylamine (572 μ L, 4.9 mmol) are added. The reaction stirred at room temperature 16 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 40% ethyl acetate/hexane) provides the title compound. ESI MS m/z 376.1 $[M + H]^+$.

Step 2

20 Methyl 3-{[ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate

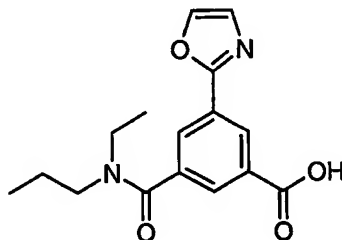


To a -70 °C stirred solution of oxazole (106 mg, 1.5 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 1.0 mL, 1.7 mmol). After 30 min, zinc chloride (1 M

in diethyl ether, 4.6 mL, 4.6 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-[[ethyl(propyl)amino]carbonyl]-5-iodobenzoate (535 mg, 1.45 mmol) in anhydrous tetrahydrofuran (1.8 mL) followed by palladium(0) tetrakis(triphenylphosphine) (120 mg, 0.10 mmol). The reaction mixture is heated at reflux for 2 h. The reaction mixture is cooled, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound. ESI MS m/z 317.1 $[M + H]^+$.

Step 3

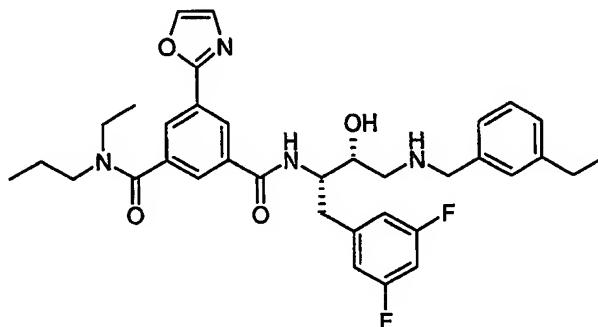
3-[[Ethyl(propyl)amino]carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid



To methyl 3-[[ethyl(propyl)amino]carbonyl]-5-(1,3-oxazol-2-yl)benzoate (375 mg, 1.2 mmol) in tetrahydrofuran/methanol/water (1:1:1, 9 mL) is added lithium hydroxide monohydrate (100 mg, 2.4 mmol), and the reaction is stirred at room temperature 16 h. The solution is diluted in chloroform and washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS m/z 301.1 $[M - H]^-$.

Step 4

N¹-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N³-ethyl-5-(1,3-oxazol-2-yl)-N³-propylisophthalamide



5

3-[[Ethyl(propyl)amino]carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (290 mg, 0.96 mmol) is dissolved in DMF (5 mL), and diisopropylethylamine (668 μ L, 3.8 mmol), HATU (438 mg, 1.15 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-
 10 [(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (391 mg, 0.96 mmol) are added. The reaction stirred at room temperature 5 h. The reaction mixture is diluted with chloroform, washed with water, 1N hydrochloric acid (aq), saturated sodium bicarbonate,
 15 saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS m/z 619.3 [M + H]⁺.

20

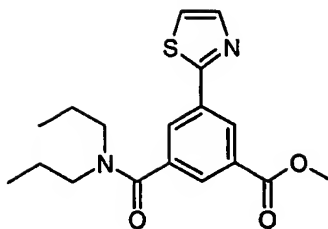
EXAMPLE SP-284

N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl)-N³,N³-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide

25

Step 1

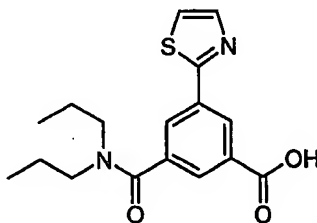
Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate



To 0.5M thiazole zinc bromide (45 mL) is added methyl 3-
[(dipropylamino)carbonyl]-5-iodobenzoate (8.6 g, 21.4 mmol) in
5 THF (130 mL), then palladium(0) tetrakis(triphenylphosphine)
(2 g, 1.7 mmol) are added. The reaction mixture is heated at
reflux for 16 h, cooled to room temperature, and then
filtered. The solution is washed with water, saturated sodium
bicarbonate, and saturated sodium chloride, dried (magnesium
10 sulfate), filtered, and concentrated under reduced pressure.
Purification by flash column chromatography (35% ethyl
acetate/hexane) yields the title compound. ESI MS m/z 347.1
[M + H]⁺.

15 Step 2

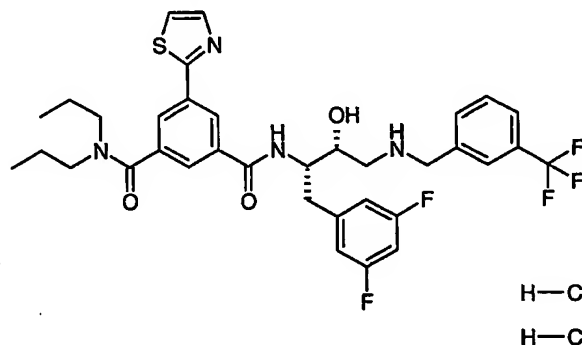
3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid



Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-
yl)benzoate (4.4 g, 12.8 mmol) is dissolved in 1:1:1
20 tetrahydrofuran/methanol/water (60 mL), and lithium hydroxide
monohydrate is added (1.1 g, 25.6 mmol), and the reaction
stirred 15 min. The solution is concentrated under reduced
pressure and diluted in chloroform. The solution is washed
with water and saturated sodium bicarbonate, dried (magnesium
25 sulfate), filtered, and concentrated under reduced pressure to
give the title compound. ESI MS m/z 333.1 [M + H]⁺.

Step 3

N¹-((1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-
 (trifluoromethyl)benzyl]amino)propyl)-N³,N³-dipropyl-5-(1,3-
 5 thiazol-2-yl)isophthalamide dihydrochloride

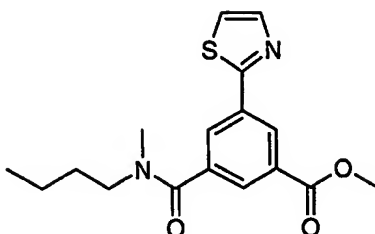


3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic
 acid is dissolved in DMF (10 mL), and diisopropylethylamine
 (364 μ L, 2.1 mmol), HATU (237 mg, 0.62 mmol), (2R,3S)-3-amino-
 10 4-(3,5-difluorophenyl)-1-[[3-
 (trifluoromethyl)benzyl]amino]butan-2-ol dihydrochloride
 prepared by the method of EXAMPLE SP-311 (250 mg, 0.52 mmol)
 are added. The reaction stirred at room temperature 4 h. The
 reaction mixture is diluted with chloroform, washed with
 15 water, saturated sodium bicarbonate, saturated sodium
 chloride, dried (sodium sulfate), filtered, and concentrated
 under reduced pressure. Purification by flash column
 chromatography (silica, 8% methanol/methylene chloride)
 provides the title compound as the free base. The residue is
 20 dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in
 diethyl ether (2 mL) is added. The mixture is concentrated
 under reduced pressure to yield the title compound. ESI MS
 m/z 689.3 [M + H]⁺.

25 EXAMPLE SP-285

Step 1

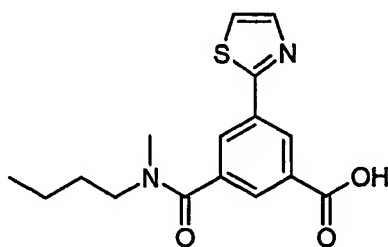
3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid



5 To 0.5M thiazole zinc bromide (4.5 mL) is added methyl 3-{[butyl(methyl)amino]carbonyl}-5-iodobenzoate (700 mg, 1.9 mmol) in THF (5 mL), then palladium(0) tetrakis(triphenylphosphine) (175 mg, 0.15 mmol) are added. The reaction mixture is heated at reflux for 16 h, cooled to
10 room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the
15 title compound. ESI MS m/z 333.1 $[M + H]^+$.

Step 2

3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid



20

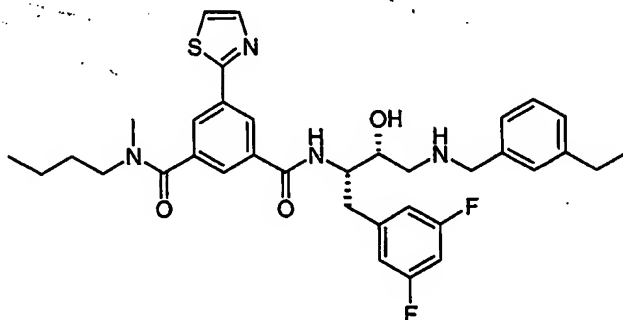
3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid (410 mg, 1.23 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate is added (103 mg, 2.5 mmol), and the reaction
25 stirred 16 h. The solution is concentrated under reduced

pressure and diluted in ethyl acetate. The solution is washed with water and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS m/z 319.1 $[M + H]^+$.

5

Step 3

N^1 -Butyl- N^3 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^1 -methyl-5-(1,3-thiazol-2-yl)isophthalamide



10

3-[[Butyl(methyl)amino]carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid (125 mg, 0.39 mmol) is dissolved in DMF (3 mL), and diisopropylethylamine (271 μ L, 1.6 mmol), HATU (178 mg, 0.47 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[[3-(trifluoromethyl)benzyl]amino]butan-2-ol dihydrochloride (176 mg, 0.43 mmol) are added. The reaction stirred at room temperature 4 h. The reaction mixture is diluted with chloroform, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 635.3 $[M + H]^+$.

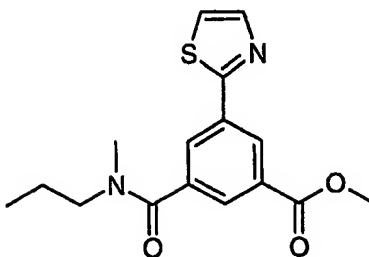
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25

EXAMPLE SP-286

Step 1

Methyl 3-{[methyl(propyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoate



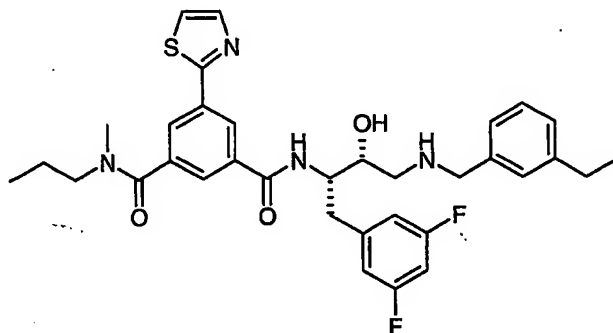
5

To 0.5M thiazole zinc bromide (4.1 mL) is added methyl 3-iodo-5-{[methyl(propyl)amino]carbonyl}benzoate (616 mg, 1.7 mmol) in THF (5 mL), then palladium(0) tetrakis(triphenylphosphine) (158 mg, 0.14 mmol) are added.

10 The reaction mixture is heated at reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash
15 column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS m/z 319.1 $[M + H]^+$.

Step 2

N^1 -{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^3 -methyl-5-(1,3-thiazol-2-yl)- N^3 -propylisophthalamide



Methyl 3-([methyl(propyl)amino]carbonyl)-5-(1,3-thiazol-2-yl)benzoate (390 mg, 1.22 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate is added (103 mg, 2.4 mmol), and the reaction
5 stirred 2 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (355 μ L, 2.0 mmol), HATU (230 mg, 0.61 mmol),
(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the
10 method of EXAMPLE SP-272 (206 mg, 0.51 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced
15 pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS m/z 621.3 $[M + H]^+$.

EXAMPLE SP-287

20

{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-dipropyl-5-pyridin-4-ylisophthalamide
dihydrochloride

25 Step 1: To a stirred solution of borate ester methyl 3-[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate dissolved in 1,4-dioxane (9.3 mL) was added sodium carbonate (2 mL of a 2 M solution in water, 4 mmol), 4-bromopyridine hydrochloride (250 mg, 1.3 mmol), and the
30 reaction mixture was degassed for 15 min. The reaction mixture was flushed with argon and heated to reflux overnight. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate (3 x 50 mL), dried (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-
[(dipropylamino)carbonyl]-5-pyridin-4-ylbenzoate (240 mg): ¹H
NMR (300 MHz, CDCl₃) δ 8.46 (d, *J* = 7 Hz, 2H), 8.10 (t, *J* = 3
5 Hz, 1H), 8.04 (t, *J* = 3 Hz, 1H), 7.97 (t, *J* = 3 Hz, 1H), 7.48
(d, *J* = 6 Hz, 2H), 3.45 (m, 2H), 3.16 (m, 2H), 2.09 (s, 3H),
1.69 (m, 2H), 1.54 (m, 2H), 0.94 (m, 3H), 0.74 (m, 3H).

Step 2: To a stirred solution of 1-methyl 3-
10 [(dipropylamino)carbonyl]-5-pyridin-4-ylbenzoate (240 mg, 0.7
mmol) in methanol (1.5 mL), tetrahydrofuran (0.7 mL), and
water (0.7 mL) was added lithium hydroxide (58 mg, 1.4 mmol).
The reaction mixture was stirred for 4 h, and concentrated
under reduced pressure. The residue was dissolved in water,
15 and extracted with ethyl acetate (3 x 75 mL). The aqueous
layer was acidified to pH 5 with 1 N hydrochloric acid and
extracted with chloroform (4 x 50 mL). The combined organic
extracts were dried (magnesium sulfate), filtered, and
concentrated under reduced pressure to provide a pyridine (160
20 mg): ¹H NMR (300 MHz, CDCl₃) δ 8.79 (d, *J* = 5 Hz, 2H), 8.45 (s,
1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.69 (d, *J* = 6 Hz, 2H), 3.50
(d, *J* = 7 Hz, 2H), 1.74 (d, *J* = 7 Hz, 2H), 1.02 (m, 3H), 0.78
(m, 3H).

25 Step 3: To a stirred solution of pyridine from step 3 (160 mg,
0.49 mmol) in dichloromethane (1.96 mL) was added DIPEA (190
mg, 1.47 mmol), HATU (278 mg, 0.73 mmol), and HOBt (99 mg,
0.73 mmol), followed by amine 2 (200 mg, 0.49 mmol). The
reaction mixture was stirred overnight at room temperature.
30 The reaction mixture was partitioned between dichloromethane
and water. The organic layer was washed with saturated sodium
bicarbonate, saturated sodium chloride, dried (magnesium
sulfate), filtered, and concentrated under reduced pressure.
The resulting oil was dissolved in a minimal amount of

methanol, and precipitated with hydrochloric acid (10 mL of a 1 M solution in diethyl ether, 10 mmol). The precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the title compound (100 mg): mp 166-169 °C; APCI MS m/z 643 $[M + H]^+$.

EXAMPLE SP-288

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(methylsulfonyl)methyl]piperidine-1-carboxamide:

Step 1: To an ice-cold, stirred solution of acid 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.4 mmol) in tetrahydrofuran (11 mL) was added borane-dimethylsulfide complex (3.4 mL of a 2.0 M solution in tetrahydrofuran, 6.8 mmol). After 2 h, the reaction mixture was quenched with methanol, and concentrated under reduced pressure to provide an alcohol (939 mg): ^1H NMR (300 MHz, CDCl_3) δ 4.11 (br s, 2H), 3.50 (t, $J = 6$ Hz, 2H), 2.68 (d, $J = 12$ Hz, 2H), 1.74-1.65 (m, 3H), 1.45 (s, 9H), 1.31 (t, $J = 7$ Hz, 1H), 1.14 (dd, $J = 12$, 4 Hz, 2H).

Step 2: To an ice-cold, stirred solution of the alcohol from step 1 (450 mg, 2.1 mmol) and triethylamine (0.32 mL, 2.3 mmol) in tetrahydrofuran (6 mL) was added methanesulfonyl chloride (0.18 mL, 2.3 mmol). The reaction mixture was stirred for 5 min and then sodium iodide (375 mg, 2.3 mmol) was added. The reaction mixture was warmed to room temperature and filtered. To the collected filtrate was added sodium thiomethoxide (161 mg, 2.3 mmol) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried

(sodium sulfate), filtered, and concentrated under reduced pressure to provide tert-butyl 4-[(methylthio)methyl]piperidine-1-carboxylate (430 mg): ¹H NMR (300 MHz, CDCl₃) δ 4.11 (t, J = 7 Hz, 2H), 2.69 (t, J = 12 Hz, 2H), 2.42 (d, J = 7 Hz, 2H), 2.10 (s, 3H), 1.83-1.78 (m, 2H), 1.66-1.59 (m, 2H), 1.45 (s, 9H), 1.26-1.06 (m, 2H).

Step 3: A solution of sulfide from step 2 (420 mg, 1.7 mmol), hydrogen peroxide (11 mL of a 30% solution in water, 170 mmol), and sodium bicarbonate (143 mg, 1.7 mmol) in acetone (10 mL) was stirred for 18 h. The reaction mixture was washed with 1.3 N sodium hydroxide, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide a sulfone (390 mg): ¹H NMR (300 MHz, CDCl₃) δ 4.11 (t, J = 7 Hz, 2H), 2.94 (s, 3H), 2.81-2.73 (m, 2H), 2.35-2.20 (m, 2H), 1.96-1.91 (m, 2H), 1.45 (s, 9H), 1.38-1.23 (m, 3H).

Step 4: A solution of sulfone from step 3 (390 mg, 1.4 mmol) and hydrochloric acid (4 mL of a 4 M solution in dioxane, 14 mmol) was stirred for 18 h. The resulting precipitate was collected by filtration to provide tert-butyl 4-[(methylsulfonyl)methyl]piperidine-1-carboxylate (220 mg): ¹H NMR (300 MHz, DMSO-d₆) δ 8.94 (br s, 1H), 8.70 (br s, 1H), 3.24-3.15 (m, 4H), 3.00 (s, 3H), 2.89 (q, J = 7 Hz, 2H), 2.29-2.18 (m, 1H), 1.97 (d, J = 13 Hz, 2H), 1.57-1.43 (m, 2H).

Step 5: To an ice-cold, stirred solution of triphosgene (108 mg, 0.36 mmol) and diisopropylethylamine (0.6 mL, 3.3 mmol) in methylene chloride (2.0 mL) was added amino sulfone from step 4 (210 mg, 0.98 mmol) in methylene chloride (3.5 mL) dropwise. After 5 min a solution of dihydrochloride of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (401 mg, 0.98 mmol) was added and the reaction mixture was warmed

until the solution became homogeneous. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), and saturated sodium chloride, dried (magnesium sulfate),
5 filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15:85 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.3 mL of a 1.0 M solution in diethyl ether, 0.3 mmol).
10 The resulting precipitate was collected by filtration to provide the title compound (38 mg): mp 130-134 °C; APCI MS m/z 538 $[M + H]^+$.

EXAMPLE SP-289

15

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methanesulfonyl)methyl]cyclohexane
carboxamide

20 Step 1: To a stirred solution of dimethyl cyclohexane-1,4-dicarboxylate (10.2 g, 51 mmol) in a mixture of 2:1:1 tetrahydrofuran/methanol/water (52 mL) was added lithium hydroxide (2.13 g, 51 mmol). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under
25 reduced pressure and the residue was partitioned between diethyl ether and water. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid, and the precipitate collected, and dried under vacuum to afford 4-(methoxycarbonyl)cyclohexanecarboxylic acid (7.4 g): 1H NMR
30 (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.33-2.27 (m, 2H), 2.11-2.06 (m, 4H), 1.50-1.43 (m, 4H).

Step 2: To an ice-cold, stirred solution of acid (3.2 g, 17 mmol) in tetrahydrofuran (40 mL) was added borane-dimethyl

sulfide complex (12 mL, 22 mmol). The reaction mixture was heated at 70 °C for 2 h and a 1:1 mixture of acetic acid/water (10 mL) added. The resulting mixture was concentrated. Purification by flash column chromatography (silica, 1:1
5 hexanes/ethyl acetate) provided methyl 4 (hydroxymethyl)cyclohexanecarboxylate (1.26 g): ¹H NMR (300 MHz, CDCl₃) δ 3.67 (s, 3H), 3.48-3.46 (m, 2H), 2.26-2.15 (m, 1H), 2.05-1.85 (m, 4H), 1.52-1.42 (m, 3H), 1.02-0.97 (m, 2H).

10 Step 3: To an ice-cold, stirred solution of the alcohol (365 mg, 2.12 mmol) and triethylamine (440 µL, 4.8 mmol) in methylene chloride (5 mL) was added mesyl chloride (200 µL, 2.6 mmol). The reaction mixture was stirred for 20 min and then partitioned between methylene chloride and water. The organic
15 layer was washed with 1 M hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), and concentrated under reduced pressure to afford the desired mesylate, which was carried on without purification or characterization.

20

Step 4: To a stirred solution of the mesylate from step 3 (2.12 mmol) in tetrahydrofuran (5 mL) was added sodium iodide (640 mg, 4.3 mmol). The reaction mixture was heated to 60 °C for 5 h and then filtered. The reaction mixture was
25 concentrated under reduced pressure, and carried on without purification or characterization.

Step 5: To a stirred solution of the iodide from step 4 (2.12 mmol) in a mixture of *N,N*-dimethylformamide (10 mL) and
30 tetrahydrofuran (1 mL) was added sodium thiomethoxide (450 mg, 6.4 mmol). The reaction mixture was heated at 70 °C for 15 h. The reaction mixture was allowed to cool to room temperature, the solvents were removed, and the residue was partitioned between ether and water. The aqueous layer was acidified to

pH 1 with 1 N hydrochloric acid, extracted with ethyl acetate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 4-[(methylthio)methyl]cyclohexanecarboxylate (230 mg): ¹H NMR (300 MHz, CD₃OD) δ 2.40-2.37 (m, 2H), 2.22-2.05 (m, 1H), 2.05 (s, 3H), 2.02-1.93 (m, 4H), 1.48-1.38 (m, 3H), 1.03-0.95 (m, 2H).

Step 6: To a stirred solution of the methyl sulfide (240 mg, 1.3 mmol) in sodium hydroxide solution (3.5 mL, 0.5 M solution) was added sodium bicarbonate (870 mg, 10.3 mmol) and acetone (1 mL) followed by the addition of a solution of oxone (1.0 g, 1.7 mmol) in 0.0004 M EDTA (4 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with sodium bisulfite. The reaction mixture was acidified with hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide acid 4-[(methylthio)methyl]cyclohexanecarboxylic acid (240 mg): ¹H NMR (300 MHz, CD₃OD) δ 3.06-3.04 (m, 2H), 2.96 (s, 3H), 2.28-2.20 (m, 1H), 2.08-1.98 (m, 5H), 1.50-1.40 (m, 2H), 1.21-1.16 (m, 2H).

Step 7: To a stirred solution of the acid (120 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (230 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) in methylene chloride (5 mL) was added *N,N*-diisopropylethylamine (340 µL, 1.93 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column

chromatography (silica, gradient 95:5 to 93:7 methylene chloride/methanol) provided the title compound (35 mg): mp 178-180 °C; ESI MS m/z 537 $[M + H]^+$.

5 EXAMPLE SP-290

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperidin-4-yl-N\ (u) 3\ (d), N\ (u) 3\ (d)-dipropylisophthalamide

10

Step 1: To a -70 °C stirred solution of N-Boc-piperidone (500 mg, 2.5 mmol) in tetrahydrofuran (11 mL) was added lithium diisopropylamine (1.37 mL of a 2 M solution in tetrahydrofuran, 2.75 mmol). The reaction mixture was stirred
15 for 2 h, warmed to 0 °C, and N-phenyltriflamide (955 mg, 2.67 mmol) was added. The solution was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate)
20 afforded tert-butyl 4-[[[(trifluoromethyl)sulfonyl]oxy]-3,6-dihydropyridine-1(2H)-carboxylate (240 mg): ^1H NMR (300 MHz, CDCl_3) δ 5.77 (s, 1H), 4.05 (m, 2H), 3.63 (m, 2H), 2.45 (m, 2H), 1.48 (s, 9H).

25 Step 2: To a stirred solution of the triflate (240 mg, 0.72 mmol) and borate ester methyl 3-[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate (280 mg, 0.72 mmol) in dioxane (3 mL) was added sodium carbonate (1.1 mL of a 2 M solution in water, 2.16 mmol). The reaction mixture was
30 flushed with argon, palladium(0) tetrakis(triphenylphosphine) (34 mg, 0.03 mmol) was added, and the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth, dried (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (90:10 chloroform/methanol) afforded an acid (160 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.11 (s, 1H), 7.95 (s, 1H), 7.58 (s, 1H), 6.15 (br s, 1H), 4.10 (s, 2H), 3.65 (m, 2H), 3.48 (m, 2H), 3.16 (s, 2H), 2.54 (s, 2H), 1.70 (s, 2H), 1.50 (s, 9H), 1.25 (m, 2H), 0.99 (s, 3H), 0.76 (s, 3H).

Step 3: A solution of the acid from step 2 (160 mg, 0.37 mmol) and 10% Pd/C (25 mg) in ethanol (10 mL) was degassed with nitrogen for 15 min, and shaken under an atmosphere of hydrogen at 50 psi for 12 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to give acid 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-5-

[(dipropylamino)carbonyl]benzoic acid (121 mg), which was carried on without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.94 (d, $J = 12$ Hz, 2H), 7.44 (s, 1H), 4.27 (br s, 2H), 3.43 (m, 2H), 3.14 (m, 2H), 2.78 (m, 4H), 1.84 (m, 3H), 1.63 (m, 6H), 1.49 (s, 9H), 1.23 (m, 3H), 0.86 (m, 3H), 0.75 (m, 3H).

Step 4: To a stirred solution of the acid (120 mg, 0.28 mmol) in methylene chloride (2 mL) was added *N,N*-diisopropylethylamine (0.141 mL, 0.84 mmol), HOBt (56 mg, 0.42 mmol), and HATU (160 mg, 0.42 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (114 mg, 0.28 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with methylene chloride (25 mL), washed with water, saturated sodium bicarbonate, and saturated sodium chloride, and dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (93:7 chloroform/methanol) afforded a piperidine (90 mg): ^1H NMR (300 MHz, CDCl_3) δ 7.61 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.14 (m,

4H), 6.79 (m, 2H), 6.64 (m, 1H), 4.29 (m, 3H), 3.68 (m, 4H), 3.47 (m, 2H), 3.02 (m, 4H), 2.77 (m, 5H), 2.66 (m, 2H), 1.71 (m, 8H), 1.48 (s, 9H), 1.24 (m, 5H), 0.99 (m, 3H), 0.73 (m, 3H).

5

Step 5: A solution of piperidine from step 4 (90 mg, 0.12 mmol) and hydrochloric acid (0.3 mL of a 4.0 M solution in dioxane, 1.2 mmol) was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure, washed with ether (50 mL), and filtered. Purification by flash column chromatography (89:10:1 chloroform/methanol/ammonium hydroxide) afforded the title compound (35 mg): mp 84-87 °C; ESI MS m/z 649 $[M + H]^+$.

15 EXAMPLE SP-291

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(1,3-oxazol-2-yl)benzamide hydrochloride

20

Step 1: To an ice-cold, stirred solution of acid 3-(methoxycarbonyl)-5-nitrobenzoic acid (24.6 g, 0.11 mol) in tetrahydrofuran (200 mL) was added borane-dimethylsulfide complex (82 mL of a 2.0 M solution in tetrahydrofuran, 0.16 mol) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, quenched with methanol, and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided an alcohol (16 g): ^1H NMR (300 MHz, DMSO- d_6) δ 8.51 (d, J = 1 Hz, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 5.69 (t, J = 6 Hz, 1H), 4.70 (d, J = 6 Hz, 2H), 3.93 (s, 3H).

Step 2: To an ice-cold, stirred solution of the alcohol from step 1 (6.6 g, 32 mmol) in methylene chloride was added phosphorus tribromide (1.5 mL, 16 mmol) and the reaction mixture was stirred for 40 min. The reaction mixture was
5 diluted with methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give a bromide (8.1 g): ^1H NMR (300 MHz, DMSO- d_6) δ 8.79 (t, J = 2 Hz, 1H), 8.45 (t, J = 2 Hz, 1H), 8.39 (d, J = 2 Hz, 1H),
10 4.57 (s, 2H), 4.00 (s, 3H).

Step 3: A solution of bromide from step 2 (8.1 g, 32 mmol) and 10% Pd/C (1.0 g) in 13:4:1 methanol/ethyl acetate/acetic acid (90 mL) was shaken under an atmosphere of hydrogen at 45 psi
15 for 24 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide 1 methyl 3-amino-5-methylbenzoate (2.8 g): ESI MS m/z 166 $[\text{M} + \text{H}]^+$.

Step 4: To an ice-cold, stirred solution of the aniline (2.8 g, 17 mmol) in 2 N hydrochloric acid (48 mL) was added a solution of sodium nitrite (1.2 g, 17 mmol) in water (10 mL), and the reaction mixture was stirred for 30 min. This reaction mixture was added to an ice-cold, stirred solution of
25 potassium iodide (5.6 g, 34 mmol) and copper(I) iodide (1.6 g, 8.6 mmol) in water (10 mL). The reaction mixture was warmed to room temperature over 2 h and then diluted with ethyl acetate. The organic layer was washed with a 10% solution of sodium thiosulfate, and saturated sodium chloride, dried
30 (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided an iodide (1.4 g): ^1H NMR (300 MHz, CDCl_3) δ 8.16 (s, 1H), 7.80 (d, J = 1 Hz, 1H), 7.72 (d, J = 1 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H).

Step 5: To a -70 °C stirred solution of oxazole (174 mg, 2.5 mmol) in tetrahydrofuran (5 mL) was added *n*-butyllithium (1.7 mL of a 1.6 M solution in hexanes, 2.8 mmol). After 30 min, zinc chloride (7.5 mL of a 1 M solution in diethyl ether, 7.5 mmol) was added and the reaction mixture was warmed to 0 °C for 1 h. To this mixture was then added iodide from step 4 (695 mg, 2.5 mmol) followed by palladium(0) tetrakis-(triphenylphosphine) (145 mg, 0.13 mmol). The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled, and diluted with ethyl acetate (50 mL). The organic layer was washed with water, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided an oxazole (330 mg): ¹H NMR (300 MHz, CD₃OD) δ 8.45 (s, 1H), 8.08 (d, *J* = 1 Hz, 1H), 8.01 (s, 1H), 7.97 (d, *J* = 1 Hz, 1H), 7.32 (s, 1H), 3.95 (s, 3H), 2.48 (s, 3H); ESI MS *m/z* 218 [M + H]⁺.

20

Step 6: To a stirred solution of the ester from step 5 (384 mg, 1.7 mmol) in methanol (5 mL) was added potassium hydroxide (15 mL of a 1.0 M solution in water, 15 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an acid (358 mg): ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.2 (br s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.42 (s, 1H), 2.45 (s, 3H).

30

Step 7: A solution of the acid from step 6 (358 mg, 1.8 mmol), HATU (1.0 g, 2.6 mmol), HOBt (357 mg, 2.6 mmol), and diisopropylethylamine (500 μ L, 2.6 mmol) was stirred in methylene chloride (2.0 mL) for 15 min. A solution of
5 dihydrochloride of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (718 mg, 1.8 mmol) and diisopropylethylamine (500 μ L, 2.6 mmol) in methylene chloride (2.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene
10 chloride, washed with 1 N hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The
15 solid was dissolved in methanol (2 mL), and treated with hydrochloric acid (0.5 mL of a 1.0 M solution in diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide the title compound (250 mg): mp 105-107 $^{\circ}$ C; APCI MS m/z 520 $[M + H]^+$.

20

EXAMPLE SP-292

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(methylsulfonyl)methyl]thiophene-2-
25 carboxamide

Step 1: To a solution of acid 5-(methoxycarbonyl)thiophene-2-carboxylic acid (1.00 g, 5.37 mmol) in tetrahydrofuran (21.5 mL) was added borane-dimethylsulfide complex (3.0 mL of a 2.0
30 M solution in tetrahydrofuran, 6.00 mmol). The reaction mixture was heated at reflux for 24 h and then carefully quenched with anhydrous methanol (1.0 mL) and cooled to room temperature. The reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The

combined organic phases were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield the desired alcohol (820 mg): ^1H NMR (300 MHz, CDCl_3) δ 7.65 (d, $J = 4$ Hz, 1H), 6.96 (d, $J = 4$ Hz, 1H),
5 4.83 (s, 2H), 3.87 (s, 3H).

Step 2: To a 0 °C solution of the alcohol prepared in step 1 (805 mg, 4.67) in tetrahydrofuran (31 mL) containing triethylamine (790 μL , 5.61 mmol) and dimethylaminopyridine (6
10 mg) was added methanesulfonyl chloride (400 μL , 5.14 mmol) and the reaction mixture was stirred for 0.5 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to provide the crude mesylate, which was used in the next step without further purification: ^1H NMR (300
15 MHz, CDCl_3) δ 7.70 (m, 1H), 7.18 (m, 1H), 5.39 (s, 2H), 3.90 (s, 3H), 2.97 (s, 3H).

Step 3: To the mesylate prepared in step 2 in *N,N*-dimethylformamide (10 mL) was added sodium thiomethoxide (516
20 mg, 7.0 mmol) and the reaction mixture was warmed to 50 °C for 18 h. The reaction was diluted with water (200 mL) and extracted with chloroform (4 x 25 mL). The combined organic phases were washed with 5% lithium chloride, water, and saturated sodium chloride, dried (sodium sulfate), filtered,
25 and concentrated under reduced pressure to give the desired sulfide (760 mg) which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, $J = 4$ Hz, 1H), 6.93 (d, $J = 4$ Hz, 1H), 3.89 (m, 5H), 2.08 (s, 3H).

30 Step 4: To a 0 °C solution of the sulfide prepared in step 3 (760 mg, 3.75 mmol) in chloroform (6.25 mL) was added 70% *m*-CPBA (2.31 g, 9.37 mmol) and the reaction stirred at 0 °C for 2.5 h. The reaction mixture was then diluted with chloroform and washed with 1 N sodium hydroxide, water, and saturated

sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the desired sulfone (780 mg) which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.74 (d, $J = 4$ Hz, 1H), 7.20 (d, $J =$
5 4 Hz, 1H), 4.46 (s, 2H), 3.89 (m, 3H), 2.87 (s, 3H).

Step 5: To a solution of the sulfone prepared in step 4 (268 mg, 1.14 mmol) in 2:1:1 dioxane/methanol/water (7.6 mL) was added lithium hydroxide monohydrate (53 mg, 1.14 mmol) and the
10 reaction mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and the solid residue was partitioned between ethyl acetate and water. The aqueous phase was acidified with 1 N hydrochloric acid and extracted several times with diethyl
15 ether. The combined ether extracts were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 5-[(methylsulfonyl)methyl]thiophene-2-carboxylic acid (115 mg) which was used without further purification: ^1H NMR (300 MHz,
20 CDCl_3) δ 7.73 (d, $J = 4$ Hz, 1H), 7.20 (d, $J = 4$ Hz, 1H), 4.52 (s, 2H), 2.90 (s, 3H); ESI MS (negative mode) m/z 219 $[\text{M} - \text{H}]^-$.

Step 6: To a solution of acid from step 5 (115 mg, 0.52 mmol) and *N,N*-diisopropylethylamine (540 μL , 3.12 mmol) in methylene
25 chloride (6.5 mL) was added HBTU (200 mg, 0.52 mmol) and the reaction mixture was stirred for 0.5 h. (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (211 mg, 0.52 mmol) was added in one portion and the reaction
30 mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography

(silica, 1-5% methanol in chloroform) gave the title compound (45 mg): mp 128-131 °C;; ESI MS m/z 537 $[M + H]^+$.

EXAMPLE SP-293

5

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-5-(1,3-thiazol-2-yl)benzamide hydrochloride

- 10 Step 1: To a -70 °C stirred solution of thiazole (214 mg, 2.5 mmol) in tetrahydrofuran (5 mL) was added *n*-butyllithium (1.7 mL of a 1.6 M solution in hexanes, 2.8 mmol). After 30 min, zinc chloride (7.5 mL of a 1 M solution in diethyl ether, 7.5 mmol) was added and the reaction mixture was warmed to 0 °C for
- 15 1 h. To this mixture was then added iodide described above (695 mg, 2.5 mmol) followed by palladium(0) tetrakis(triphenylphosphine) (145 mg, 0.13 mmol). The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled and diluted with ethyl acetate (50 mL).
- 20 The organic layer was washed with water, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided a thiazole (208 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.38
- 25 (s, 1H), 8.02 (d, J = 1 Hz, 1H), 7.92 (s, 1H), 7.88 (d, J = 3 Hz, 1H), 7.37 (d, J = 3 Hz, 1H), 3.95 (s, 3H), 2.48 (s, 3H).

- Step 2: To a stirred solution of the ester from step 1 (208 mg, 0.89 mmol) in 2:1:1 methanol/tetrahydrofuran/water (4 mL)
- 30 was added lithium hydroxide (75 mg, 1.8 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted

with chloroform (5 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an acid (146 mg): ^1H NMR (300 MHz, DMSO- d_6) δ 13.17 (br s, 1H), 8.28 (s, 1H), 8.01 (d, J = 1 Hz, 1H), 7.96 (d, J = 3 Hz, 1H), 7.85 (d, J = 3 Hz, 2H), 2.45 (s, 3H).

Step 3: A solution of the acid from step 2 (140 mg, 0.64 mmol), HATU (364 mg, 0.96 mmol) and diisopropylethylamine (170 μL , 0.96 mmol) was stirred in methylene chloride (2.0 mL) for 15 min. A solution of dihydrochloride (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (318 mg, 0.64 mmol) and diisopropylethylamine (170 μL , 0.96 mmol) in methylene chloride (2.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.5 mL of a 1.0 M solution in diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide the title compound (100 mg): mp 178-180 $^{\circ}\text{C}$; APCI MS m/z 536 $[\text{M} + \text{H}]^+$.

EXAMPLE SP-293

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)methyl]cyclohexanecarboxamide

Step 1: To an ice-cold, stirred solution of cyclohexane-1,4-dicarboxylic acid (3.0 g, 17 mmol) in a mixture of 2:1 tetrahydrofuran/methanol (24 mL) was added trimethylsilyl diazomethane (9 mL of a 2.0 M in hexanes, 18 mmol). The
5 reaction mixture was stirred at room temperature for 2 h. Acetic acid (5 mL) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 10:1:0.01 hexanes/ethyl acetate/acetic acid) provided 4-(methoxycarbonyl)cyclohexanecarboxylic acid (1.00 g): ¹H NMR
10 (300 MHz, CDCl₃) δ 3.68 (s, 3H), 2.53-2.47 (m, 2H), 1.97-1.89 (m, 4H), 1.74-1.66 (m, 4H).

Step 2: To an ice-cold, stirred solution of acid from step 1 (700 mg, 3.8 mmol) in tetrahydrofuran (10 mL) was added
15 borane-dimethyl sulfide complex (2 mL, 4.1 mmol). The reaction mixture was warmed to room temperature for 2 h and a 1:1 mixture of acetic acid/water (10 mL) was added. The resulting mixture was concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1
20 hexanes/ethyl acetate) provided methyl 4-(hydroxymethyl)cyclohexanecarboxylate (560 mg): ¹H NMR (500 MHz, CDCl₃) δ 3.68 (s, 3H), 3.51-3.46 (m, 2H), 2.59-2.57 (m, 1H), 2.05-2.00 (m, 2H), 1.65-1.55 (m, 5H), 1.31-1.27 (m, 2H).

25 Step 3: To an ice-cold, stirred solution of alcohol from step 2 (300 mg, 1.8 mmol) and triethylamine (370 μL, 2.7 mmol) in methylene chloride (5 mL) was added mesyl chloride (170 μL, 2.1 mmol). The reaction mixture was stirred for 20 min and then partitioned between methylene chloride and water. The organic
30 layer was washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), and concentrated under reduced pressure to afford the desired mesylate, which was carried on without purification or characterization.

Step 4: To a stirred solution of the mesylate from step 3 (1.8 mmol) in tetrahydrofuran (5 mL) was added sodium iodide (530 mg, 3.5 mmol). The reaction mixture was heated at 60 °C for 5 h, cooled to room temperature, and then filtered. The reaction mixture was concentrated under reduced pressure, and carried on without purification or characterization.

Step 5: To a stirred solution of the iodide from step 4 (1.8 mmol) in a mixture of *N,N*-dimethylformamide (10 mL) and tetrahydrofuran (1 mL) was added sodium thiomethoxide (375 mg, 5.3 mmol). The reaction mixture was heated at 70 °C for 15 h. The reaction mixture was then cooled to room temperature, the solvents were removed, and the residue partitioned between ether and water. The aqueous layer was acidified to pH 1 with 1 N hydrochloric acid, extracted with ethyl acetate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford 4-[(methylthio)methyl]cyclohexanecarboxylic acid (50 mg): ¹H NMR (300 MHz, CD₃OD) δ 2.53-2.51 (m, 1H), 2.43-2.41 (m, 3H), 2.05 (s, 3H), 2.05-1.95 (m, 2H), 1.71-1.53 (m, 4H), 1.36-1.30 (m, 2H).

Step 6: To a stirred solution of methyl sulfide from step 5 (100 mg, 0.5 mmol) in sodium hydroxide solution (1.5 mL, 0.5 M solution in water) was added sodium bicarbonate (360 mg, 4.3 mmol) and acetone (1 mL) followed by the addition of a solution of oxone (430 mg, 0.7 mmol) in 0.0004 M EDTA (2 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with sodium bisulfite. The reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 4-[(methylsulfonyl)methyl]cyclohexanecarboxylic acid (100 mg): ¹H

NMR (300 MHz, CD₃OD) δ 3.11-3.08 (m, 2H), 2.96 (s, 3H), 2.53-2.51 (m, 1H), 2.18-2.16 (m, 1H), 1.99-1.93 (m, 2H), 1.79-1.25 (m, 6H).

5 Step 7: To a stirred solution of acid from step 6 (100 mg, 0.5 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (190 mg, 0.5 mmol), and HATU (175 mg, 0.5 mmol) in methylene chloride (5 mL) was added *N,N*-diisopropylethylamine (280 μ L, 1.6 mmol). The reaction mixture
10 was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column
15 chromatography (silica, gradient 95:5 to 92:8 methylene chloride/methanol) provided the title compound (60 mg): mp 45-50 °C; ESI MS *m/z* 537 [M + H]⁺.

EXAMPLE SP-293

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N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperidin-3-yl-*N,N*-dipropylisophthalamide hydrochloride

25 Step 1: To a stirred solution of 3-bromo-pyridine (205 mg, 1.3 mmol) and methyl 3-[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate (500 mg, 1.3 mmol) in dioxane (9 mL) was added sodium carbonate (2.0 mL of a 2 M solution in water, 3.9 mmol). The reaction mixture was flushed with
30 argon, palladium(0) tetrakis(triphenylphosphine) (36 mg, 0.052 mmol) was added and the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth, dried (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (3:2 hexanes/ethyl acetate) afforded a pyridine (200 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.88 (m, 1H), 8.65 (m, 1H), 8.31 (m, 1H), 8.07 (m, 1H), 7.92 (m, 1H), 7.79 (m, 1H), 7.67 (m, 1H), 3.98 (m, 3H), 3.50 (m, 2H), 3.21 (m, 2H), 1.66 (m, 4H), 1.07 (m, 3H), 0.78 (m, 3H).

Step 2: A solution of the pyridine from step 1 (160 mg, 0.37 mmol) and platinum oxide (15 mg) in ethanol (2.5 mL), water (0.5 mL), and concentrated hydrochloric acid (1.0 mL) was degassed with nitrogen for 15 min, and shaken under an atmosphere of hydrogen at 50 psi for 12 h. The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to afford methyl 3-[(dipropylamino)carbonyl]-5-piperidin-3-ylbenzoate (204 mg, quantitative), which was carried forward without further purification: ^1H NMR (300 MHz, CDCl_3) δ 9.62 (m, 3H), 8.02 (m, 3H), 4.78 (m, 2H), 3.96 (s, 3H), 3.61 (m, 5H), 2.04 (m, 5H), 1.34 (m, 3H), 0.91 (m, 6H).

20

Step 3: To a stirred solution of piperidine from step 2 (204 mg, 0.59 mmol) in methylene chloride (1.6 mL) was added Boc anhydride (162 mg, 0.65 mmol) and triethylamine (0.122 mL, 0.88 mmol). The solution was stirred at room temperature for 2 d. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded a Boc-protected piperidine (100 mg): ^1H NMR (300 MHz, CDCl_3) δ 7.93 (t, $J = 3$ Hz, 1H), 7.88 (t, $J = 3$ Hz, 1H), 7.42 (t, $J = 3$ Hz, 1H), 4.16 (m, 2H), 3.93 (s, 3H), 3.46 (m, 2H), 3.13 (m, 2H), 2.78 (m, 3H), 2.03 (d, $J = 10$ Hz, 1H), 1.70 (m, 7H), 1.48 (m, 9H), 1.00 (m, 3H), 0.75 (m, 3H).

30

Step 4: To a stirred solution of piperidine from step 3 (100 mg, 0.22 mmol) in methanol (2 mL) was added potassium

hydroxide (2.2 mL of a 1 M solution in water, 2.2 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was acidified to pH
5 4-5 with 1 N hydrochloric acid and extracted with chloroform (5 x 50 mL). The combined organic layers were dried (magnesium sulfate), filtered, and concentrated under reduced pressure to afford an acid (90 mg): ¹H NMR (300 MHz, CDCl₃) δ 7.99 (s, 1H), 7.94 (s, 1H), 7.47 (s, 1H), 4.12 (m, 2H), 3.47
10 (m, 2H), 3.14 (m, 2H), 2.77 (m, 3H), 2.03 (m, 1H), 1.67 (m, 7H), 1.48 (s, 9H), 0.98 (m, 3H), 0.77 (m, 3H).

Step 5: To a stirred solution of piperidine from step 4 (90 mg, 0.21 mmol) in methylene chloride (1 mL) was added *N,N*-
15 diisopropylethylamine (0.142 mL, 0.84 mmol), HOBt (42 mg, 0.31 mmol), and HATU (118 mg, 0.31 mmol) followed by (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-
ol (86 mg, 0.21 mmol). The reaction was stirred for 16 h at room temperature. The reaction mixture was diluted with
20 methylene chloride (25 mL), washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (95:5 chloroform/methanol) afforded a piperidine (100 mg) which was
25 carried forward without further characterization.

Step 6: A solution of piperidine from step 5 (100 mg, 0.15 mmol) and hydrochloric acid (0.4 mL of a 4.0 M solution in dioxane, 1.5 mmol) was stirred for 30 min at room temperature.
30 The reaction mixture was concentrated under reduced pressure and washed with ether (50 mL). The precipitate that formed was collected by filtration to give the title compound (60 mg): mp 145-145 °C; ESI MS *m/z* 649 [M + H]⁺.

EXAMPLE SP-294

1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-1H-pyrrole-2-carboxamide

Step 1: To a stirred solution of ethanol (54 mL) was added sodium metal (1.29 g, 54.00 mmol). The reaction mixture was stirred for 1 h and then diethyl acetamidomaloate (2.37 g, 10.92 mmol) was added. The reaction mixture was heated at reflux for 1 h and 1,4-dichloro-2-butyne (1.14 mL, 11.64 mmol) was added. The reaction mixture was refluxed for 1 h, cooled to room temperature, and concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), treated with activated charcoal, filtered through diatomaceous earth, and concentrated under reduced pressure to yield ethyl 5-methyl-1H-pyrrole-2-carboxylate (1.26 g): ^1H NMR (300 MHz, CDCl_3) δ 8.82 (br s, 1H), 6.81 (s, 1H), 5.95 (s, 1H), 4.31 (q, J = 6 Hz, 2H), 2.31 (s, 3H), 1.34 (t, J = 6 Hz, 3H).

Step 2: A mixture of pyrrole from step 1 (240 mg, 1.71 mmol), potassium carbonate (306 mg, 2.21 mmol), and butyl bromide (328 mg, 2.39 mmol) in acetonitrile (10 mL) was heated to 40 °C for 2 d. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a brown oil. Purification by flash column chromatography (silica, 5.5:1 hexanes/ethyl acetate) gave an ester (232 mg): ^1H NMR (300 MHz, CDCl_3) δ 6.91 (d, J = 3 Hz, 1H), 5.88 (d, J = 3 Hz, 1H), 4.24

(m, 4H), 2.26 (s, 3H), 1.65 (m, 2H), 1.37 (m, 5H), 0.99 (m, 3H); ESI MS m/z 210 $[M + H]^+$.

Step 3: A mixture of the ester from step 2 (232 mg, 1.11 mmol) and 3:1:1 methanol/tetrahydrofuran/2 N sodium hydroxide (5 mL) was stirred overnight. The reaction was not complete after 24 h. The reaction mixture was heated to 40 °C for 4 h, cooled to room temperature, and then partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 1-butyl-5-methyl-1H-pyrrole-2-carboxylic acid (110 mg): ^1H NMR (300 MHz, CDCl_3) δ 7.04 (d, J = 3 Hz, 1H), 5.93 (d, J = 3 Hz, 1H), 4.24 (m, 2H), 2.28 (s, 3H), 1.67 (m, 2H), 1.43 (m, 2H), 0.99 (m, 3H).

Step 4: To a stirred solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (248 mg, 0.608 mmol), acid (110 mg, 0.608 mmol), HOBt (82 mg, 0.608 mmol), and *N*-methylemorpholine (99 mg, 2.43 mmol) in methylene chloride (5 mL) was added EDC (210 mg, 1.09 mmol). The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 methylene chloride/methanol) gave the title compound (100 mg): mp 116-121 °C; ESI MS m/z 498 $[M + H]^+$.

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EXAMPLE SP-295

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-pyrrol-2-ylmethyl)amino]propyl}-5-methyl-*N,N*-dipropylisophthalamide

Step 1: A mixture of tert-butyl (1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (170 mg, 0.538 mmol), 1H-pyrrole-2-carbaldehyde (51 mg, 0.538 mmol), and triethylamine (60 mg, 0.592 mmol) was stirred in chloroform (10 mL) containing magnesium sulfate for 4 h. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was dissolved in 2-propanol (10 mL) and sodium borohydride (26 mg, 0.699 mmol) was added. The reaction mixture was stirred overnight and then treated with methanol. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gave tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-pyrrol-2-ylmethyl)amino]propylcarbamate (132 mg): ¹H NMR (300 MHz, CD₃OD) δ 6.82 (m, 4H), 6.21 (s, 1H), 6.09 (m, 1H), 4.09 (s, 2H), 3.66 (m, 2H), 3.19 (m, 1H), 3.13 (m, 1H), 3.03 (m, 1H), 2.88 (m, 1H), 1.31 (s, 9H).

Step 2: To a stirred solution of the pyrrole from step 1 (132 mg, 0.334 mmol) in dioxane (3 mL) was added hydrochloric acid (0.33 mL, 4 N dioxane, 1.34 mmol). The reaction mixture was stirred overnight and then concentrated under reduced pressure to give an amine (134 mg, quantitative) as a brown solid, which was used without any further characterization or purification.

Step 3: To a stirred mixture of the amine from step 2 (134 mg, 0.334 mmol), 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (88 mg, 0.334 mmol), HOBt (45 mg, 0.334 mmol), and N-methylmorpholine (203 mg, 2.00 mmol) in methylene chloride (5 mL) was added EDC (115 mg, 0.601 mmol). After 24 h, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric

acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (silica, 9:1:1 methylene chloride/methanol/ammonium hydroxide) gave the title compound (27 mg): mp 63-74 °C; ESI MS m/z 541 $[M + H]^+$.

EXAMPLE SP-296

10 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-piperazin-1-yl-N,N-dipropylisophthalamide hydrochloride

Step 1: In a sealed tube, a solution of dimethyl 5-bromoisophthalate (5.0 g, 18.3 mmol), N-benzylpiperazine (4.0 mL, 23.0 mmol), and cesium carbonate (8.4 g, 25.7 mmol) in toluene (36 mL) was degassed with nitrogen at room temperature for 20 minutes. Palladium (II) acetate (225 mg, 0.92 mmol) and BINAP (1.7 g, 2.74 mmol) were quickly added under nitrogen and the solution heated to 80 °C overnight to yield a yellow solution with a white suspension. The reaction mixture was cooled to room temperature, vacuum filtered, and the solid rinsed with fresh toluene. The filtrate was then concentrated under reduced pressure to yield a yellow oil. Purification by flash chromatography (silica, 80:20 hexanes/ethyl acetate) gave the desired dimethyl 5-(4-benzylpiperazin-1-yl)isophthalate (4.40 g): ESI MS m/z 369 $[M + H]^+$.

Step 2: To a solution of the ester from step 1 (1.0 g, 2.70 mmol) in 2:1:1 dioxane/methanol/water (18 mL) was added lithium hydroxide monohydrate (100 mg, 2.44 mmol) and the reaction mixture stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water.

The organic layer was set aside and the aqueous phase acidified with 1 N hydrochloric acid and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the desired monoacid (945 mg): ^1H NMR (300 MHz, CDCl_3) δ 10.50-10.30 (br s, 1H), 8.19-8.12 (m, 1H), 7.80-7.60 (m, 2H), 7.35-7.26 (m, 5H), 3.91 (s, 3H), 3.73 (s, 2H), 3.36-3.33 (m, 4H), 2.77-2.71 (m, 4H); ESI MS m/z 355 $[\text{M} + \text{H}]^+$.

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Step 3: To a solution of the monoacid prepared in step 2 (1.2 g, 3.38 mmol) in methylene chloride (22.5 mL) was added triethylamine (940 μL , 6.76 mmol), *N,N*-dipropylamine (554 μL , 4.0 mmol), and 2-chloro-1-methylpyridinium iodide (865 mg, 3.38 mmol). The reaction mixture was stirred at room temperature overnight. The residue was then diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a yellow oil. Purification by flash column chromatography (silica, 80:20 hexanes/ethyl acetate) gave the desired amide (1.0 g): ^1H NMR (300 MHz, CDCl_3) δ 7.59-7.58 (m, 1H), 7.44-7.42 (m, 1H), 7.35-7.26 (m, 5H), 7.05-7.04 (m, 1H), 3.89 (s, 3H), 3.56 (s, 2H), 3.50-3.35 (m, 2H), 3.28-3.25 (m, 4H), 3.20-3.05 (m, 2H), 2.62-2.58 (m, 4H), 1.70-1.40 (m, 4H), 1.00-0.95 (m, 3H), 0.80-0.70 (m, 3H).

Step 4: To a solution of the amide prepared in step 3 (1.00 g, 2.28 mmol) in absolute ethanol (120 mL) was added palladium(II) hydroxide (100 mg) and the reaction shaken under 55 psi of hydrogen at 60 $^\circ\text{C}$ overnight. The reaction was then cooled to room temperature, filtered through diatomaceous earth, and the filter cake rinsed with fresh ethanol. The filtrate was concentrated under reduced pressure and

redissolved in dry acetonitrile (15 mL). To this was added di-tert-butyl dicarbonate (650 mg, 2.96 mmol) and *N,N*-diisopropylethylamine (450 μ L, 2.50 mmol), and the reaction mixture stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure, redissolved in chloroform, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless oil.

Purification by flash column chromatography (silica, 66:33 hexanes/ethyl acetate) yielded the desired Boc-protected amine (953 mg): ^1H NMR (300 MHz, CDCl_3) δ 7.60–7.59 (m, 1H), 7.48–7.47 (m, 1H), 7.08–7.07 (m, 1H), 3.92 (s, 3H), 3.60–3.51 (m, 4H), 3.46–3.44 (m, 2H), 3.22–3.16 (m, 6H), 1.70–1.48 (m, 13H), 1.10–0.98 (m, 3H), 0.78–0.74 (m, 3H); ESI MS m/z 448 $[\text{M} + \text{H}]^+$.

Step 5: To a solution of Boc-protected amine prepared in step 4 (953 mg, 2.13 mmol) in 2:1:1 dioxane/methanol/water (14.2 mL) was added lithium hydroxide monohydrate (268 mg, 6.39 mmol), and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and then partitioned between ethyl acetate and water. The aqueous phase was acidified with 1 N hydrochloric acid and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the desired 3-[4-(tert-butoxycarbonyl)piperazin-1-yl]-5-[(dipropylamino)carbonyl]benzoic acid (770 mg): ESI MS m/z 434 $[\text{M} + \text{H}]^+$.

Step 6: A solution of the acid from step 5 (320 mg, 0.738 mmol) and HBTU (279 mg, 0.738 mmol) in methylene chloride (4.6 mL) containing *N,N*-diisopropylethylamine (770 μ L, 4.42 mmol)

was stirred at room temperature for 20 minutes. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (300 mg, 0.738 mmol) and *N,N*-diisopropylethylamine (770 μ L, 4.42 mmol) in methylene chloride (4.6 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure, diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a yellow syrup. Purification by flash column chromatography (silica, 93:7 chloroform/methanol) gave the desired amide (443 mg): ESI MS m/z 750 $[M + H]^+$.

Step 7: To a solution of the amide prepared in step 6 (220 mg, 0.293 mmol) in 1,4-dioxane (2.0 mL) was added hydrochloric acid (750 μ L, 4 M dioxane, 3.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then concentrated under reduced pressure. The residue was taken up in methylene chloride and concentrated again under reduced pressure. This was repeated until a solid remained. No further purification was required. The recovered solid was dried under high vacuum over phosphorus pentoxide at 50 °C for 48 h to give the title compound (120 mg) which was characterized as its dihydrochloride salt: mp 135-136 °C; ESI MS m/z 650 $[M + H]^+$.

EXAMPLE SP-297

N-{(1*S*,2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxo-4-propylcyclohexyl)acetamide

Step 1: A solution of 2-propylphenol (26.83 g, 197 mmol), potassium carbonate (30.64 g, 221 mmol), methyl iodide (50.0

mL, 800 mmol), and 18-crown-6 (500 mg, 1.9 mmol) in acetone (300 mL) was refluxed for 48 h. The reaction mixture was cooled to room temperature, the solid removed by filtration, and the filtrate concentrated under reduced pressure. The
5 resulting residue was partitioned between methylene chloride and water. The organic layer was washed with 2 N sodium hydroxide, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford the desired methyl phenyl ether (23.46 g) as an oil,
10 which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.16–7.11 (m, 2H), 6.90–6.82 (m, 2H), 3.81 (s, 3H), 2.58 (m, 2H), 1.60 (tq, $J = 7, 5$ Hz, 2H), 0.95 (t, $J = 7$ Hz, 3H).

15 Step 2: Absolute ethanol (200 mL) followed by tetrahydrofuran (50 mL) was added at -78°C to a solution of methyl phenyl ether from step 1 (10.0 g, 66.58 mmol) suspended in anhydrous ammonia (700 mL). Lithium metal (2.3 g, 330 mmol) was added at -78°C in small portions over 0.5 h to yield a deep blue
20 solution. The reaction was stirred at -78°C until a white solution resulted. The cooling bath was taken away, the flask exposed to the atmosphere, and the ammonia was removed under a stream of nitrogen. The solid residue remaining was dissolved in a minimum amount of water and acidified to pH 3 with 10%
25 hydrochloric acid, and then extracted several times with diethyl ether. The combined ether phase was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and carefully concentrated under reduced pressure at 0°C to provide an oil. The oil was dissolved in 10% hydrochloric
30 acid (200 mL) and refluxed for 3 h. The reaction mixture was then cooled to room temperature and extracted several times with diethyl ether. The combined ether extracts were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an

oil. Purification by flash column chromatography (silica, 89:11 hexanes/ethyl acetate) gave 2-propylcyclohexenone (4.43 g): ^1H NMR (300 MHz, CDCl_3) δ 6.95-6.89 (m, 1H), 5.97 (app dt, $J = 10, 2$ Hz, 1H), 2.39-2.36 (m, 3H), 2.20-2.04 (m, 1H), 1.88-1.63 (m, 2H), 1.50-1.25 (m, 4H), 0.93 (t, $J = 7$ Hz, 3H).

Step 3: A solution of sodium metal (30 mg, 1.30 mmol) in absolute ethanol (4.0 mL) was stirred at -10°C for 0.5 h. Diethyl malonate (3.5 mL, 23 mmol) was added at -10°C followed by addition of a solution of 2-propylcyclohexenone (3.0 g, 21.7 mmol) in absolute ethanol (3.0 mL). The reaction mixture was stirred an additional 12 h at room temperature. The reaction mixture was acidified to pH 3 with 10% hydrochloric acid and then extracted several times with diethyl ether. The combined ether extracts were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a yellow oil. Purification by flash column chromatography (silica, 83:17 hexanes/ethyl acetate) gave 2-(3-oxo-4-propylcyclohexyl)-malonic acid diethyl ester (5.07g): ^1H NMR (300 MHz, CDCl_3) δ 4.21 (q, $J = 7$ Hz, 2H), 4.20 (q, $J = 7$ Hz, 2H), 3.30 (s, 0.5H), 3.28 (s, 0.5H), 2.67-1.55 (m, 8H), 1.43-1.11 (m, 10H), 0.90 (t, $J = 7$ Hz, 1.5H), 0.90 (t, $J = 7.0$ Hz, 1.5H).

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Step 4: A solution of the diester from step 2 (2.37 g, 7.94 mmol) in 1 N potassium hydroxide (16.27 mL, 16.27 mmol) was refluxed for 2 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride. The aqueous phase was acidified to pH 1-2 with 6 N hydrochloric acid and then refluxed for 2 h. The reaction mixture was cooled to room temperature and extracted several times with methylene chloride. The combined organic phase was washed with water, and saturated sodium chloride, dried

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(sodium sulfate), filtered, and concentrated under reduced pressure to yield a light yellow oil. Purification by flash column chromatography (silica, 66:33 hexanes/ethyl acetate with 1% glacial acetic acid) gave (3-oxo-4-propyl-cyclohexyl)-
5 acetic acid (1.42 g): ^1H NMR (300 MHz, CDCl_3) δ 2.71-1.12 (m, 14H), 1.11-0.82 (m, 3H); ESI MS m/z 197 $[\text{M} - \text{H}]^-$.

Step 5: To a stirred solution of the acid from step 4 (244 mg, 1.23 mmol) and *N,N*-diisopropyl ethylamine (214 μL , 1.23 mmol)
10 in methylene chloride (7.0 mL) was added HBTU (513 mg, 1.35 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution of amine (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (500 mg, 1.35 mmol) and *N,N*-diisopropylethylamine (428 μL , 2.46
15 mmol) in methylene chloride (7.0 mL) and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, 0.5 N hydrochloric acid, and saturated sodium chloride. The organic layer was then
20 dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 7:93 methanol/methylene chloride) gave the title compound (360 mg): mp 52-54 $^\circ\text{C}$; ESI MS m/z 515 $[\text{M} + \text{H}]^+$.

25

EXAMPLE SP-298

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxocyclohexyl)acetamide

30

Step 1 (3-Oxo-cyclohexyl)-malonic acid diethyl ester was prepared in 88% yield from cyclohexenone by the method described above for the synthesis of 2-(3-oxo-4-propyl-

cyclohexyl)-malonic acid diethyl ester: ^1H NMR (300 MHz, CDCl_3) δ 4.44-4.12 (m, 4H), 2.88-1.22 (m, 16H).

Step 2 (3-Oxo-cyclohexyl)-acetic acid was prepared in 70%
5 yield from 2-(3-oxo-cyclohexyl)-malonic acid diethyl ester by
the method described above for the synthesis of (3-oxo-4-
propyl-cyclohexyl)-acetic acid: ^1H NMR (300 MHz, CDCl_3) δ 2.58-
1.92 (m, 7H), 1.80-1.61 (m, 1H), 1.52-1.42 (m, 1H); ESI MS m/z
155 $[\text{M} - \text{H}]^-$.

10

Step 3: $\text{N}-\{(1\text{S}, 2\text{R})-1-(3,5\text{-difluorobenzyl})-3-[(3\text{-ethylbenzyl)amino}] -2\text{-hydroxypropyl})-2-(3\text{-oxocyclohexyl)acetamide}$ was prepared in 23% yield from (3-Oxo-cyclohexyl)-acetic acid by the method described for the
15 synthesis of $\text{N}-\{(1\text{S}, 2\text{R})-1-(3,5\text{-difluorobenzyl})-3-[(3\text{-ethylbenzyl)amino}] -2\text{-hydroxypropyl})-2-(3\text{-oxo-4-propylcyclohexyl)acetamide}$ (EXAMPLE SP-297.)
 $\text{mp } 139.5\text{-}149.8\text{ }^\circ\text{C}$; ESI MS m/z 473 $[\text{M} + \text{H}]^+$.

20 EXAMPLE SP-299

3-benzyl-4-(4-butylphenyl)- $\text{N}-\{(1\text{S}, 2\text{R})-1-(3,5\text{-difluorobenzyl})-3-[(3\text{-ethylbenzyl)amino}] -2\text{-hydroxypropyl})-4\text{-oxobutanamide}$

25 Step 1: Benzaldehyde (2.81 mL, 27.15 mmol) was added at 0 $^\circ\text{C}$ to
a solution of 4-butyl-acetophenone (5.26 mL, 27.15 mmol) in
methanol (7.8 mL) and water (13.0 mL) containing sodium
hydroxide (1.39 g, 34.75 mmol). The reaction was warmed to
room temperature and stirred 48 h. The reaction mixture was
30 diluted with ethyl acetate and washed with water, saturated
sodium chloride, dried (sodium sulfate), filtered, and
concentrated to yield a light yellow syrup. Volatile
impurities were removed under high vacuum at 120 $^\circ\text{C}$ to yield
the desired enone (6.3 g): ESI MS m/z 265 $[\text{M} + \text{H}]^+$.

Step 2: A solution of the enone prepared in step 1 (2.0 g, 7.56 mmol) in anhydrous diethyl ether (11 mL) was added at -78 °C to a solution of lithium metal (120 mg, 16.6 mmol) in dry liquid ammonia (11 mL). The reaction was stirred at -78 °C for 0.5 h and excess lithium was quenched with several drops of piperylene to yield a yellow solution. Lithium bromoacetate (2.75 g, 18.9 mmol) was added in one portion and the reaction stirred at -78 °C for 0.5 h then at -33 °C for 2 h. The reaction was then quenched with NH₄Cl and the open reaction vessel warmed to room temperature. The residue was partitioned between ethyl acetate and water and the phases separated. The organic phase was washed with water, saturated sodium chloride, dried (sodium sulfate), filtered and concentrated to yield a yellow syrup. Purification by flash column chromatography (silica, 74:25:1 hexanes/ethyl acetate/acetic acid) gave 3-benzyl-4-(4-butylphenyl)-4-oxobutanoic acid (60 mg): ESI MS *m/z* 325 [M + H]⁺.

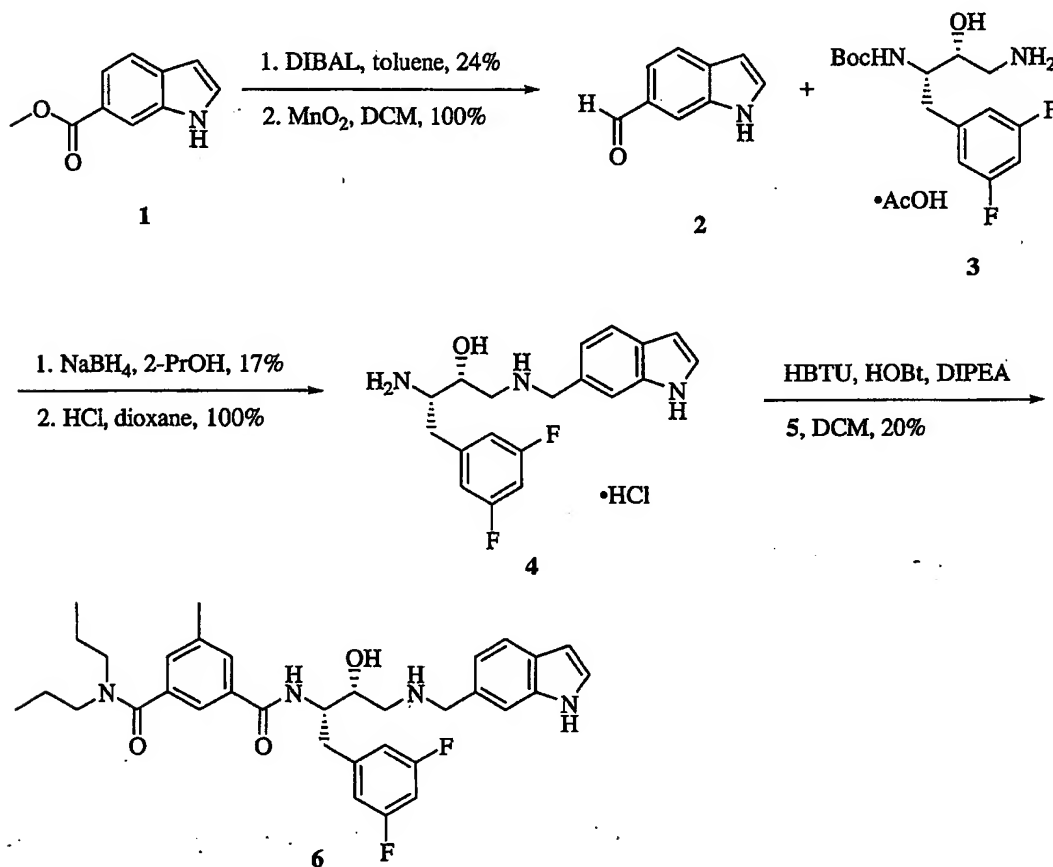
Step 3: A solution of 3-benzyl-4-(4-butylphenyl)-4-oxobutanoic acid (60 mg, 0.185 mmol) and HBTU (70 mg, 0.185 mmol) in methylene chloride (1.2 mL) containing *N,N*-diisopropylethylamine (100 µL, 0.55 mmol) was stirred at room temperature for 20 minutes. To this was added a solution of amine (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (75 mg, 0.185 mmol) and *N,N*-diisopropylethylamine (100 µL, 0.55 mmol) in methylene chloride (1.2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure, diluted with methylene chloride, washed with saturated sodium bicarbonate, water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless syrup. Purification by flash column chromatography (silica,

93:7 chloroform/methanol) gave the title compound (36 mg) (diastereomeric mixture): mp 42-45 °C; ESI MS m/z 641 $[M + H]^+$.

EXAMPLE SP-300

5

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-indol-6-ylmethyl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide



10

Step 1: To a -78 °C, stirred solution of methyl 1H-indole-6-carboxylate (500 mg, 2.85 mmol) in methylene chloride (11.5 mL) was added diisobutylaluminum hydride (5.70 mL, 1.0 M solution in methylene chloride). The reaction mixture was stirred for 2 h at -78 °C, and slowly warmed to room temperature for 10 h. The reaction mixture was quenched with methanol, washed with Rochelle's salt (saturated aqueous

potassium sodium tartrate), dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 6:1 ethyl acetate/hexanes) afforded an alcohol (100 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.21 (br s, 1H), 7.62 (d, $J = 9$ Hz, 1H), 7.39 (s, 1H), 7.20–7.22 (m, 1H), 7.10–7.13 (m, 1H), 6.54–6.56 (m, 1H), 4.77 (d, $J = 3$ Hz, 2H), 1.60 (s, 1H).

Step 2: To a stirred solution of alcohol from step 1 (100 mg, 0.68 mmol) in methylene chloride (3 mL) was added magnesium oxide (590 mg, 6.8 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to provide 1H-indole-6-carbaldehyde (99 mg) as a solid, which was carried forward without further purification or characterization. ^1H NMR (300 MHz, CDCl_3) δ 10.03–10.88 (m, 1H), 8.56 (br s, 1H), 7.96 (s, 1H), 7.74 (d, $J = 8$ Hz, 1H), 7.64–7.70 (m, 1H), 7.46 (t, $J = 3$ Hz, 1H), 6.65 (s, 1H).

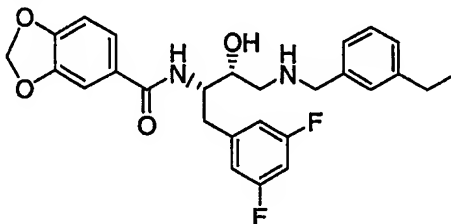
Step 3: To a stirred solution of 1H-indole-6-carbaldehyde (99 mg, 0.68 mmol) and tert-butyl (1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate acetate **3** (256 mg, 0.68 mmol) in 2-propanol (3 mL) was added sodium borohydride (30 mg, 0.82 mmol). The reaction mixture was stirred for 12 h., quenched with methanol, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided indole (50 mg): ^1H NMR (300 MHz, CDCl_3) δ 8.41 (br s, 1H), 7.60 (d, $J = 8$ Hz, 1H), 7.38 (s, 1H), 7.21 (t, $J = 3$ Hz, 1H), 7.04 (dd, $J = 8$, 1 Hz, 1H), 6.71–6.73 (m, 3H), 6.61–6.68 (m, 1H), 6.53 (s, 1H), 5.38 (br s, 2H), 4.66 (d, $J = 9$ Hz, 1H), 3.89 (s, 2H), 3.49–3.54 (m, 1H), 2.91–2.98 (m, 1H), 2.62–2.73 (m, 3H), 1.35 (s, 9H).

Step 4: To a stirred solution of indole from step 3 (50 mg, 0.11 mmol) was added hydrochloric acid (0.27 mL, 4.0 M solution in dioxane). The reaction mixture was stirred for 1 h, diluted with ethyl ether, and concentrated under reduced pressure to provide (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1H-indol-6-ylmethyl)amino]butan-2-ol hydrochloride **4** (70 mg): ESI MS m/z 346 $[M + H]^+$.

Step 5: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (**5**) (29 mg, 0.11 mmol) in methylene chloride (3 mL) was added HBTU (64 mg, 0.17 mmol), HOBT (23 mg, 0.17 mmol), and *N,N*-diisopropylethylamine (0.075 mL, 0.44 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1H-indol-6-ylmethyl)amino]butan-2-ol hydrochloride **4** (70 mg, 0.11 mmol). The reaction mixture was stirred for 12 h, diluted with methylene chloride, washed with water, saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 89:10:1 chloroform/methanol/ammonium hydroxide) provided the title compound (**6**) (13 mg): mp 135-137 °C; ESI MS m/z 591 $[M + H]^+$.

EXAMPLE SP-301

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-benzodioxole-5-carboxamide

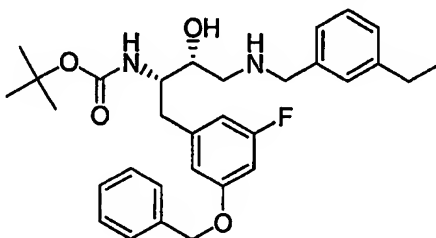


To a solution of piperonylic acid (0.500g, 3.01 mmol), EDC (0.867g, 4.52 mmol), HOBT (0.611g, 4.52 mmol) in anhydrous DMF (10 mL) was added a solution of TEA (1.67 mL, 12.04 mmol), 3-Amino-4-(3,5-difluoro-phenyl)-1-(3-ethyl-benzylamino)-butan-

2-ol (1.693g, 3.01 mmol), and anhydrous DMF (5 mL). Reaction mixture was stirred under nitrogen overnight. Quenched reaction mixture with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate. Washed organic layer with 1N HCl, followed by a wash with 10% sodium bicarbonate (aq.). Dried organic layer over magnesium sulfate, filtered, then concentrated in vacuo, yielding the product. (ES+: 483.2)

EXAMPLE SP-302

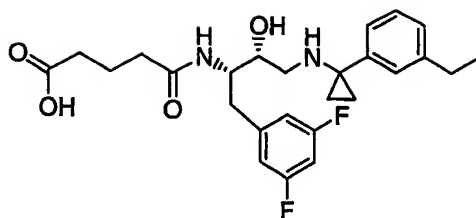
tert-butyl (1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-3-[(3-ethylbenzyl)amino]-2-hydroxypropylcarbamate



[2-(3-Benzyloxy-5-fluoro-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester (3.33 g, 8.59 mmol) and m-ethyl benzylamine (2.32 g, 17.19 mmol) were dissolved in isopropyl alcohol (80 ml) and brought to reflux for 2h. Reaction mixture was then concentrated in vacuo to remove isopropyl alcohol. Dissolved yellow liquid in ethyl acetate (30 ml), then washed with 1N HCl (3x100 ml). Aqueous layers were combined then extracted with ethyl acetate (2x100 ml). Organic layers were washed with 10% sodium bicarbonate (aq., 3x100 ml), followed by a brine wash. Organic layer was dried over sodium sulfate, filtered, then concentrated in vacuo, yielding the product (4.31 g). (ES+: 523.9)

EXAMPLE SP-303

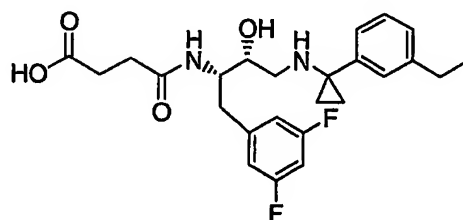
5-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]amino]-5-oxopentanoic acid



To a solution of 3-Amino-4-(3,5-difluoro-phenyl)-1-[1-(3-ethyl-phenyl)-cyclopropylamino]-butan-2-ol (0.500g, 1.387 mmol) in chloroform (7 ml) was added TEA (0.58 ml, 4.161 mmol) with stirring under nitrogen for 30 min. To this solution was added glutaric anhydride (0.158g, 1.387 mmol) and reaction was stirred overnight at 50°C. The reaction mixture was concentrated in vacuo, yielding the product. (ES+: 475.2)

EXAMPLE SP-304

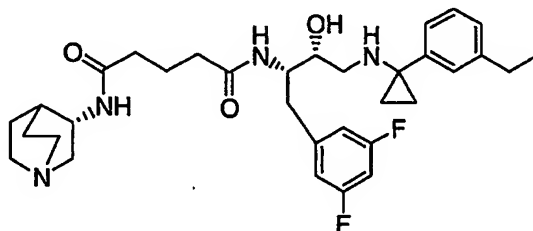
4-[(1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl]amino]-4-oxobutanoic acid



To a solution of 3-Amino-4-(3,5-difluoro-phenyl)-1-[1-(3-ethyl-phenyl)-cyclopropylamino]-butan-2-ol (0.500g, 1.387 mmol) in chloroform (7 ml) was added TEA (0.58 ml, 4.161 mmol) with stirring under nitrogen for 30 min. To this solution was added succinic anhydride (0.138g, 1.387 mmol) and reaction was stirred overnight at 50°C. The next morning reaction mixture was concentrated in vacuo, yielding the product. (ES+: 461.2)

EXAMPLE SP-305

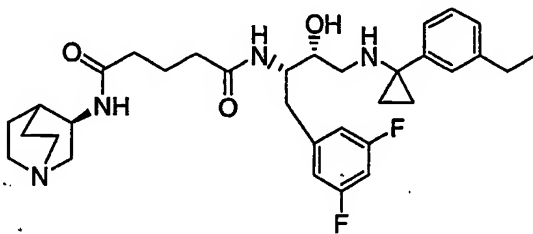
formic acid compound with N¹-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)pentanediamide (1:1)



To a solution of R-aminoquinuclidine (0.084g, 0.421 mmol) TEA (0.294 ml, 2.11 mmol), and anhydrous DMF (2.5 ml) was added 5-(((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)amino)-5-oxopentanoic acid (0.200g, 0.421 mmol), EDC (0.121g, 0.632 mmol), HOBT (0.085g, 0.632 mmol) under nitrogen, with stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.122g). Prep-HPLC yielded the product as its formate salt. (ES+: 583.3)

EXAMPLE SP-306

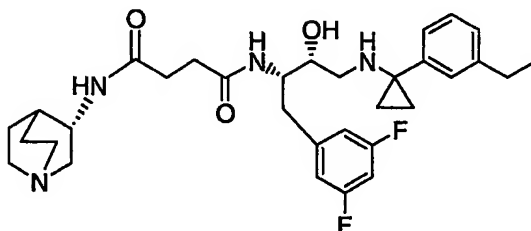
formic acid compound with N¹-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)pentanediamide (1:1)



To a solution of S-aminoquinuclidine (0.084g, 0.421 mmol) TEA (0.294 ml, 2.11 mmol), and anhydrous DMF (2.5 ml) was added
 5 5-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]amino]-5-oxopentanoic acid (0.200g, 0.421 mmol), EDC (0.121g, 0.632 mmol), HOBT (0.085g, 0.632 mmol) under nitrogen, with stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.065g). Prep-
 10 HPLC yielded the product as its formate salt. (ES+: 583.3)

EXAMPLE SP-307

formic acid compound with N¹-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)succinamide
 15 (1:1)

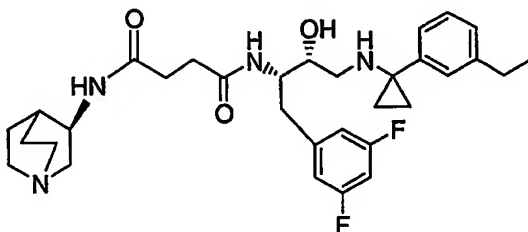


To a solution of R-aminoquinuclidine (0.086g, 0.434 mmol) TEA (0.302 ml, 2.17 mmol), and anhydrous DMF (2.5 ml) was added
 20 4-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]amino]-4-oxobutanoic acid (0.200g, 0.434 mmol), EDC (0.125g, 0.651 mmol), and HOBT (0.088g, 0.651 mmol) under nitrogen, with
 25 stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.200g). Prep-HPLC yielded the product as its formate salt. (ES+: 569.3)

EXAMPLE SP-308

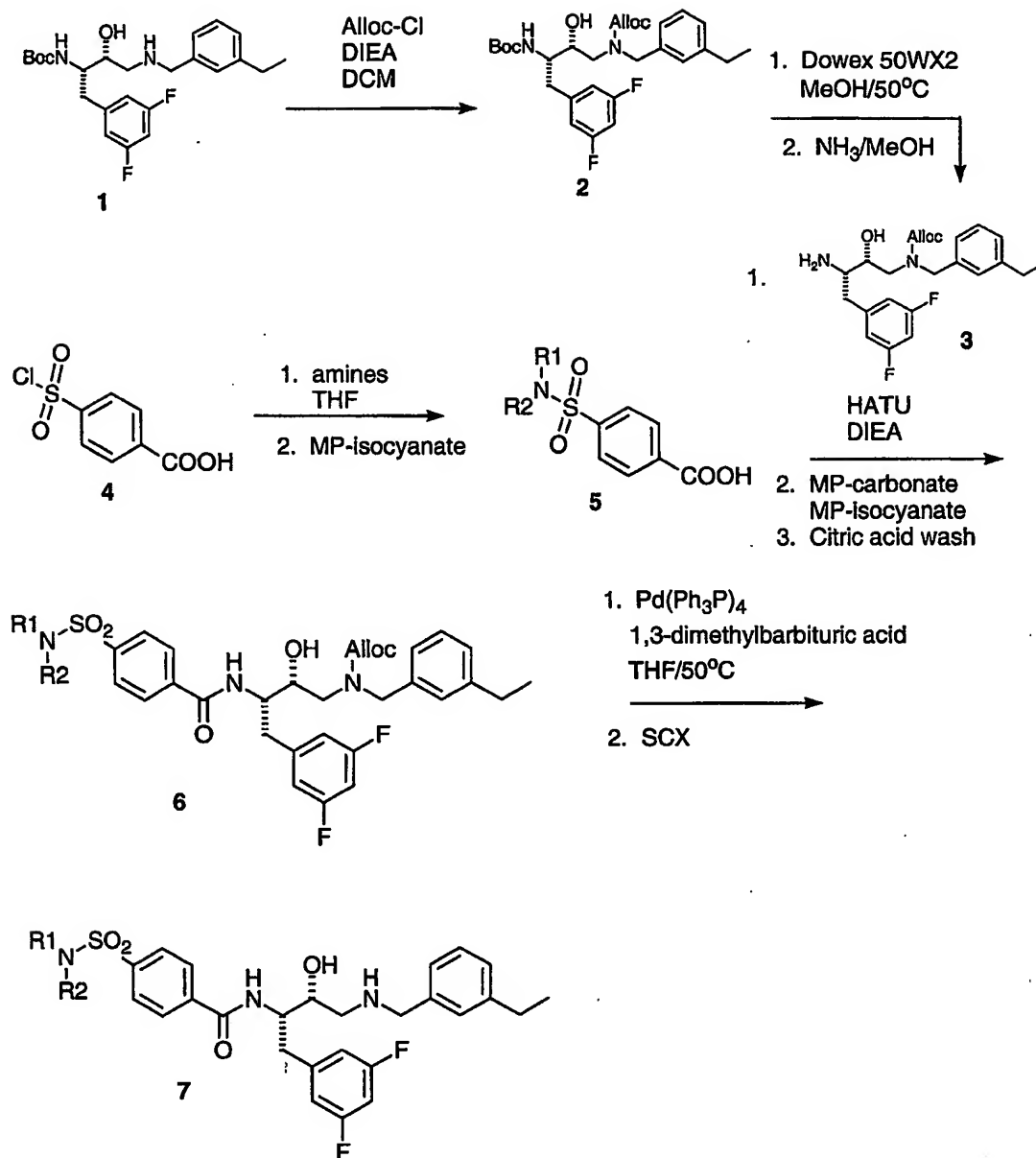
formic acid compound with N¹-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)succinamide

5 (1:1)



To a solution of S-aminoquinuclidine (0.086g, 0.434 mmol)
 10 TEA (0.302 ml, 2.17 mmol), and anhydrous DMF (2.5 ml) was added
 4-(((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino)-4-oxobutanoic acid (0.200g, 0.434 mmol), EDC (0.125g, 0.651 mmol), and HOBT (0.088g, 0.651 mmol) under nitrogen, with
 15 stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.093g). Prep-HPLC yielded the product as its formate salt. (ES+: 569.3)

EXAMPLE SP-309



MP stands for macroporous resin.

2: A solution of **1** (2.50g; 5.75mmol) and DIEA (1.20mL; 6.90mmol) in DCM (100mL) was cooled in an ice/water bath. Allyl chloroformate (0.73mL; 6.90mmol) was added, and the reaction was allowed to come to ambient temperature over 4h. The reaction was washed with 10% K₂CO₃ (100mL), water (100mL), brine (100mL), and dried over Na₂CO₃. Flash chromatography on 90g silica gel with 0-30% EtOAc/ heptane afforded 2.88g (5.55mmol; 96%) **2** as a white solid.

3: A solution of 2 (2.88g; 5.55mmol) and Dowex 50WX2 (Aldrich; 8.88g; approx. 44.4mmol) in MeOH (100mL) was heated to 50°C for 5.25h. The reaction was cooled to ambient temperature and filtered. The resin was washed well with MeOH, and the product was eluted with approx. 3.5M ammonia in MeOH. After removal of solvent, 2.11g (5.04mmol; 91%) 3 was collected as an off-white waxy solid.

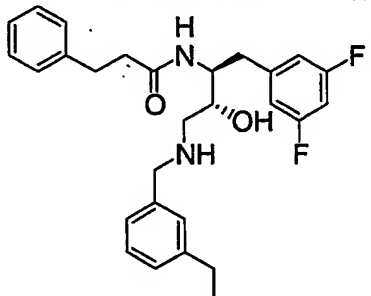
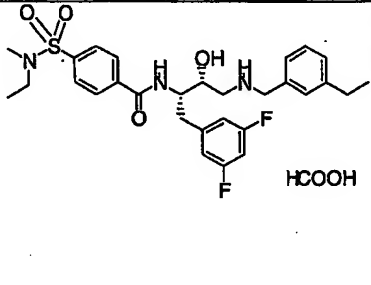
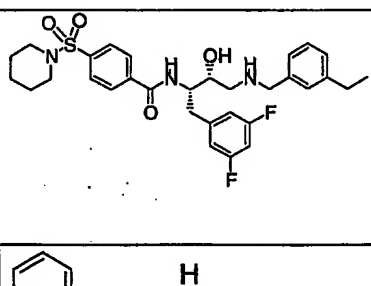
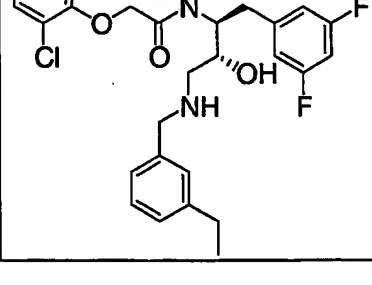
5: The appropriate amines (0.3mmol) were added to vials containing 4-(chlorosulfonyl)benzoic acid 4 (2.0mL of a 0.05M solution of THF) plus 1eq. of DIEA if necessary (to liberate any amine hydrochloride salts). The vials were agitated on an orbital shaker at ambient temperature/250rpm for 18h. MP-isocyanate resin (approx. 0.6mmol) was added to each vial, which were heated to 60°C for 5h. The reactions were filtered, the resin washed well with THF, and concentrated.

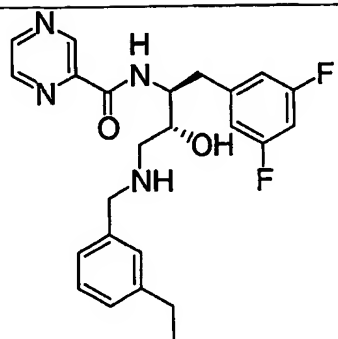
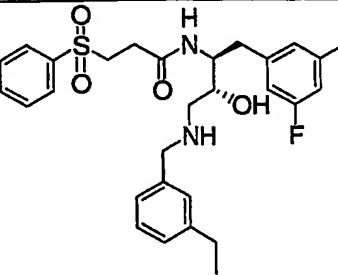
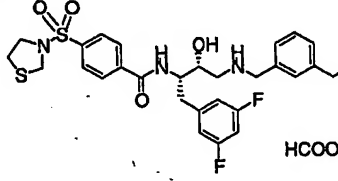
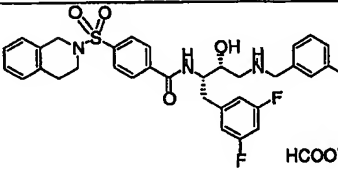
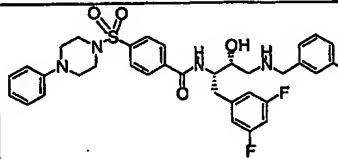
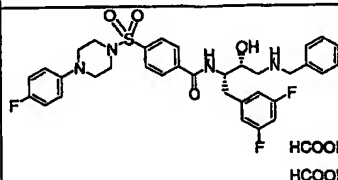
6: The acids 5 were coupled to Alloc-protected TSI 3 using HATU (1.2eq.) and DIEA (2.4eq.) in DMF for 18h at ambient temperature. MP-isocyanate (3eq.) and MP-carbonate (1eq.) were then added, and the reactions rocked for 4h at ambient temperature. The reactions were filtered, the resins washed well with 1,2-dichloroethane, and concentrated. The residues were dissolved in 1,2-dichloroethane (1.5mL), washed with 1M citric acid (1.5mL) and loaded onto 3mL capacity Varian ChemElut Hydromatrix cartridges. After 5 min, the product was eluted with 1,2-dichloroethane (2x6mL), and concentrated in vacuo.

7: Alloc intermediates 6 were deprotected using Pd(Ph₃P)₄ (0.15eq.) and 1,3-dimethylbarbituric acid (20eq.) in THF at 60°C/3h. The reaction vials were concentrated in vacuo, and SCX was performed by loading the crude reaction mixture onto

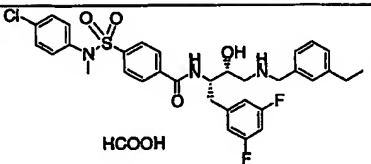
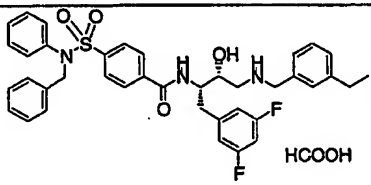
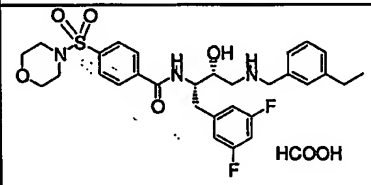
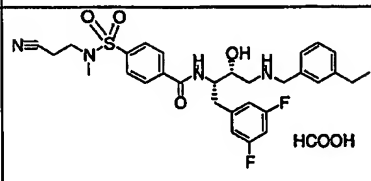
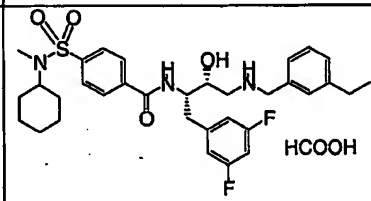
1000mg/3mL SCX cartridges using 5mL MeOH. The cartridges were washed well with MeOH, and the products eluted with approx. 3.5M ammonia in MeOH. If necessary, the final products were purified by high-throughput preparative UV HPLC.

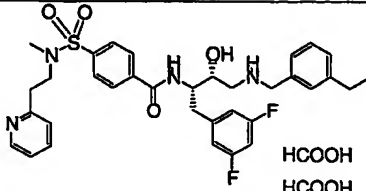
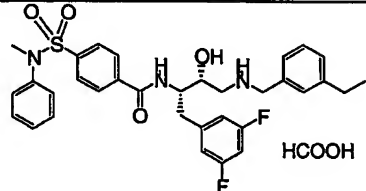
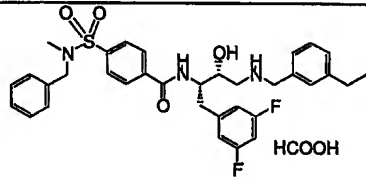
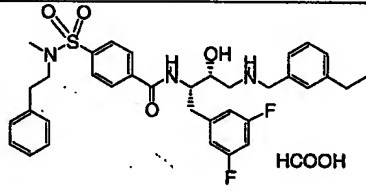
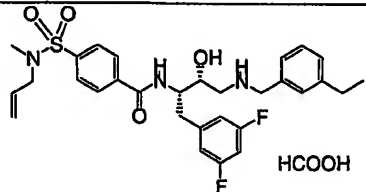
- 5 The following compounds were prepared using the above described methodology.

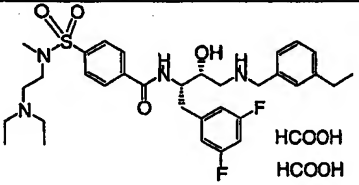
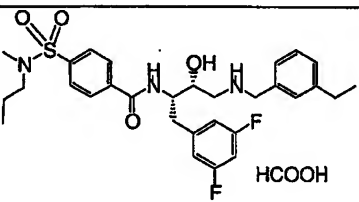
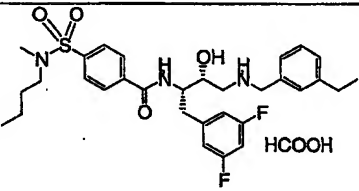
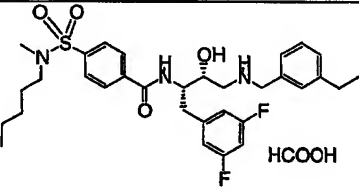
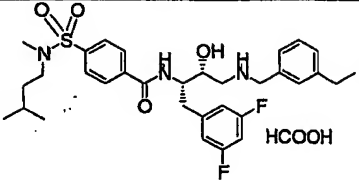
EXAMPLE	Structure	Compound Name(s)	OAMS
2965		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-phenylpropanamide	467.3
2966		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-([ethyl(methyl)amino]sulfonyl)benzamide (1:1)	560.1
2967		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(piperidin-1-ylsulfonyl)benzamide	586.2
2968		2-(2-chlorophenoxy)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	503.3

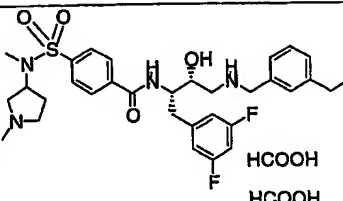
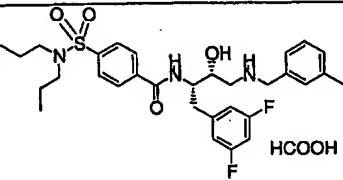
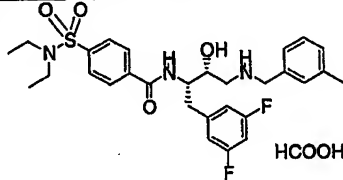
2969		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)pyrazine-2-carboxamide	441.2
2970		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(phenylsulfonyl)propanamide	531.2
2971		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-thiazolidin-3-ylsulfonyl)benzamide (1:1)	589.9
2972		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzamide (1:1)	634.0
2973		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(4-phenylpiperazin-1-yl)sulfonyl]benzamide	663.0
2974		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(4-phenylpiperazin-1-yl)sulfonyl]benzamide (1:1)	680.9

		hydroxypropyl}-4-{[4-(4-fluorophenyl)piperazin-1-yl]sulfonyl}benzamide (2:1)	
2975		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(pyrrolidin-1-ylsulfonyl)benzamide	572
2976		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(pyrrolidin-1-ylsulfonyl)benzamide (1:1)	572.0
2977		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-({4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)benzamide (2:1)	731.0
2978		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(dimethylamino)sulfonyl]benzamide	546
2979		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(dimethylamino)sulfonyl]benzamide (1:1)	546.0

2980		formic acid compound with 4-[[4-chlorophenyl] (methyl) amino]sulfonyl}-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}benzamide (1:1)	642.0
2981		formic acid compound with 4-[[benzyl (phenyl) amino]sulfonyl}-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}benzamide (1:1)	684.1
2982		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(morpholin-4-ylsulfonyl)benzamide (1:1)	588.1
2983		formic acid compound with 4-[[2-cyanoethyl] (methyl) amino]sulfonyl}-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}benzamide (1:1)	585.0
2984		formic acid compound with 4-[[cyclohexyl (methyl) amino]sulfonyl}-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}benzamide (1:1)	614.0

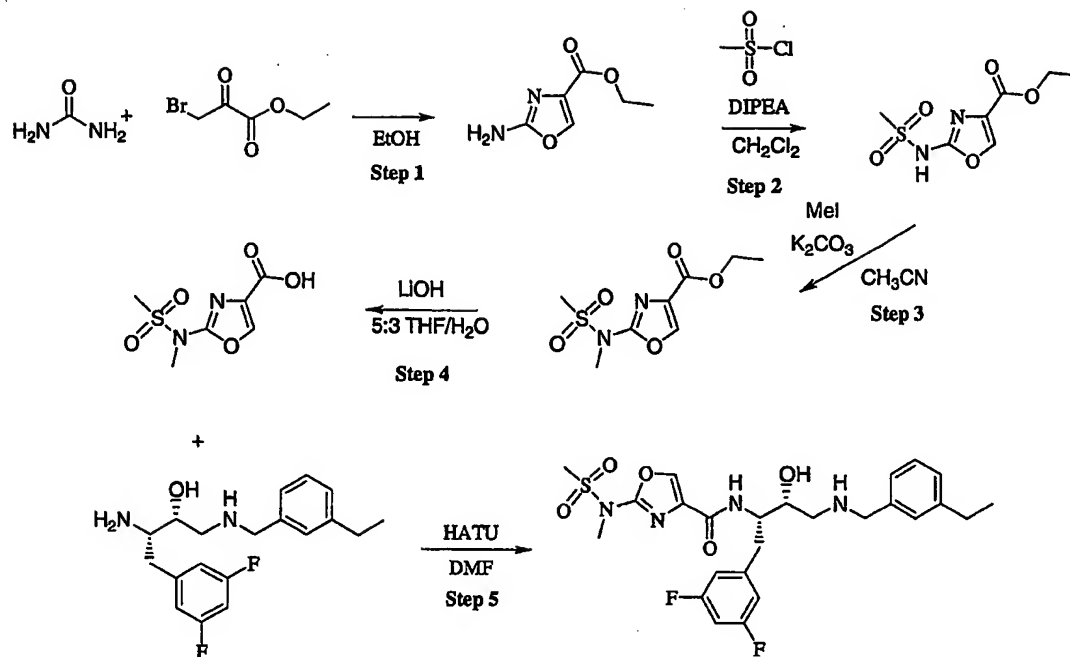
2985	 <p>Chemical structure of a formic acid compound. It features a pyridine ring attached to a sulfonamide group, which is further connected to a 3,5-difluorobenzyl group. The structure is labeled with HCOOH and HCOOH.</p>	formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(2-pyridin-2-ylethyl)amino]sulfonyl]benzamide (2:1)	637.0
2986	 <p>Chemical structure of a formic acid compound. It features a phenyl ring attached to a sulfonamide group, which is further connected to a 3,5-difluorobenzyl group. The structure is labeled with HCOOH.</p>	formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(phenyl)amino]sulfonyl]benzamide (1:1)	608.1
2987	 <p>Chemical structure of a formic acid compound. It features a phenyl ring attached to a sulfonamide group, which is further connected to a 3,5-difluorobenzyl group. The structure is labeled with HCOOH.</p>	formic acid compound with 4-[[benzyl(methyl)amino]sulfonyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide (1:1)	622.1
2988	 <p>Chemical structure of a formic acid compound. It features a phenyl ring attached to a sulfonamide group, which is further connected to a 3,5-difluorobenzyl group. The structure is labeled with HCOOH.</p>	formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(2-phenylethyl)amino]sulfonyl]benzamide (1:1)	636.1
2989	 <p>Chemical structure of a formic acid compound. It features a phenyl ring attached to a sulfonamide group, which is further connected to a 3,5-difluorobenzyl group. The structure is labeled with HCOOH.</p>	formic acid compound with 4-[[allyl(methyl)amino]sulfonyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide (1:1)	572.1

2990		formic acid compound with 4-[[2-(diethylamino)ethyl](methyl)amino]sulfonyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (2:1)	631.1
2991		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(propyl)amino]sulfonyl}benzamide (1:1)	574.1
2992		formic acid compound with 4-[[butyl(methyl)amino]sulfonyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (1:1)	588.1
2993		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(pentyl)amino]sulfonyl}benzamide (1:1)	602.1
2994		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[isopentyl(methyl)amino]sulfonyl}benzamide (1:1)	602.1

2995		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(1-methylpyrrolidin-3-yl)amino]sulfonyl]benzamide (2:1)	615.0
2996		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(dipropylamino)sulfonyl]benzamide (1:1)	602.0
2997		formic acid compound with 4-[(diethylamino)sulfonyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide (1:1)	574.0

EXAMPLE SP-310

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide



ethyl 2-amino-1,3-oxazole-4-carboxylate

Step 1. To a 250 ml 3-neck round bottom flask was added (20g, 0.3332 moles) urea, (150ml) ethanol and (42.42g, 0.2175 moles, 0.65eq) ethylbromopyruvate. The mixture was then heated under agitation to reflux for 16 hours. The reaction solution changed from yellow to red in color. The reaction solution was then evaporated to dryness and the crude product was taken up in (50ml) water and (150ml) ethyl acetate. The pH was adjusted from 1 to 10 using 2N sodium hydroxide, changing the biphasic mixture a dark red. The mixture was separated and the aqueous phase was extracted twice with ethyl acetate. The organic layers were then combined and washed with water and brine. The resulting yellow solution was concentrated to ~50ml, causing an off-white solid to precipitate out. The solid was filtered off and washed with ethanol and diethyl ether. The mother liquor was then evaporated to dryness and the resulting oily solid was taken up in (150ml) ethyl acetate and concentrated to ~50ml. An off-white solid precipitated out. The mixture was cooled in an ice bath, and the solid was filtered off and washed with

ethanol and diethyl ether to give ethyl 2-amino-1,3-oxazole-4-carboxylate (14.79 g).

ethyl 2-[(methanesulfonyl)amino]-1,3-oxazole-4-carboxylate

5 Step 2. To a 20 ml screw cap vial was added (1g, 5.8069 mmol) ethyl 2-amino-1,3-oxazole-4-carboxylate, (10ml) dichloromethane and (1.39ml, 7.9797mmol, 1.25 eq.) N,N-diisopropylethylamine. To the reaction was then added (0.545ml, 7.0415 mmol, 1.1 eq.) methanesulfonyl chloride, 10 and the reaction was agitated for 14 hours. The reaction was then evaporated to dryness and purified using a Biotage silica gel column, resulting in (272mg) of ethyl 2-[(methanesulfonyl)amino]-1,3-oxazole-4-carboxylate.

15 ethyl 2-[methyl(methanesulfonyl)amino]-1,3-oxazole-4-carboxylate

Step 3. To a 25 ml round bottom flask under N₂ was added (101.8mg, 0.4346 mmol) ethyl 2-[(methanesulfonyl)amino]-1,3-oxazole-4-carboxylate, (180.2mg, 1.3038 mmol, 3.0 eq.) 20 potassium carbonate, and (5ml) acetonitrile. The mixture was then agitated at ambient temperature while (33.8μl, 0.5429 mmol, 1.25 eq.) iodomethane was added. The reaction was allowed to run at ambient temperature for 3 hours. An electrospray mass spec indicated mostly starting material. 25 The N₂ line was removed and an additional (40μl, 0.6425 mmol, 1.5 eq.) iodomethane were added. The reaction was left at ambient temperature overnight. The reaction was quenched with (5ml) 1N HCl and was extracted with dichloromethane. The organic layer was washed with water and then evaporated to 30 dryness. The resulting oil was purified by preparative HPLC, yielding (70mg) of ethyl 2-[methyl(methanesulfonyl)amino]-1,3-oxazole-4-carboxylate.

2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxylic acid

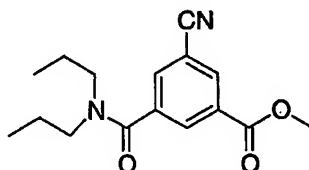
Step 4. To a 50 ml round bottom flask was added (61mg, 0.2457 mmoles) ethyl 2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxylate, (51.5mg, 1.2274 mmoles, 5.0 eq.) lithium hydroxide, (2.5ml) tetrahydrofuran and (1.5ml) water. The reaction was agitated at ambient temperature for ~2 hours. The reaction was complete by electrospray mass spec. The reaction was worked up by adding (5ml) 1N HCl and then extracting with ethyl acetate. The organic layer was washed with water and brine and then dried with magnesium sulfate. The solution was then evaporated to dryness, leaving (44.6mg) of 2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxylic acid.

15 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide

Step 5. To a 7 ml screw cap vial was added (20.9mg, 0.0949 mmoles) 2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxylic acid, (36.7mg, 0.1097 mmoles, 1.15 eq.) (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol and (54.6mg, 0.1436 mmoles, 1.5 eq.) HATU, followed by (1.25ml) N,N-dimethylformamide. The reaction was placed in an orbital shaker and was left at ambient temperature for 2 hours. The reaction was quenched with (2ml) 1N HCl. The clear solution was extracted three times with ethyl acetate and the combined organic layers were washed with saturated sodium carbonate solution and then brine. The solution was then dried with magnesium sulfate and evaporated to a clear oil which was purified by preparative HPLC, resulting N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide (15.7mg).

EXAMPLE SP-311

methyl 3-cyano-5-[(dipropylamino)carbonyl]benzoate



5

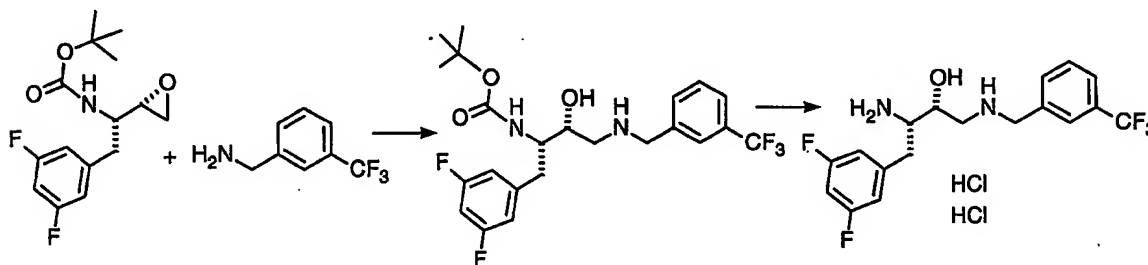
Methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (Preparation 3) (0.15 g), copper (I) cyanide, and N-methylpyrrolidinone (1 mL) was heated at 150 °C overnight, at which time the mixture was cooled and partitioned between ethyl acetate and aq. HCl (1N). The organic layer was dried (magnesium sulfate), concentrated under reduced pressure, and the residue was chromatographed on silica gel using ethyl acetate-hexane (20/80) to give 0.066 g of the desired product. ms (m + H) 289.2. See also preparation 7 for the preparation of the acid.

15

EXAMPLE SP-312

(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride

20



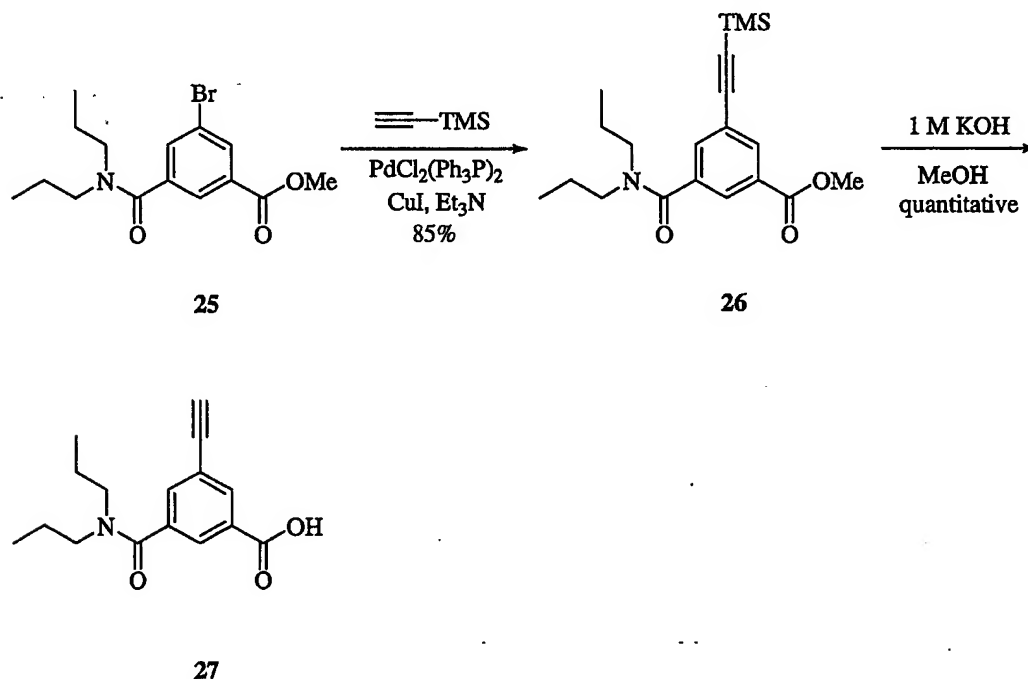
A mixture of oxirane (1.0 g) and 3-(trifluoromethyl)benzylamine (1.2 g) in isopropyl alcohol (25 mL) was stirred at reflux for 4 h, at which time the mixture was cooled and the solvent was removed under reduced pressure.

The residue was partitioned between ethyl acetate and aq. HCl (1N) and the organic layers were dried (sodium sulfate), concentrated, and chromatographed on silica gel using methanol-dichloromethane (5/95) to give 1.0 g of tert-butyl
 5 (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propylcarbamate.

The carbamate group was then removed essentially using the method described in EXAMPLE SP-272.

10 EXAMPLE SP-313

3-[(dipropylamino)carbonyl]-5-ethynylbenzoic acid



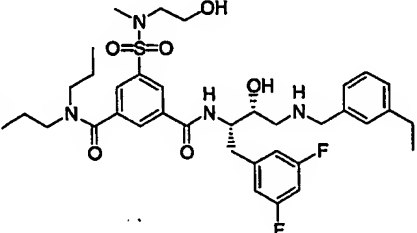
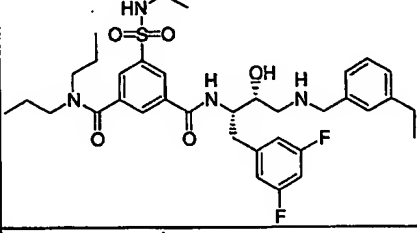
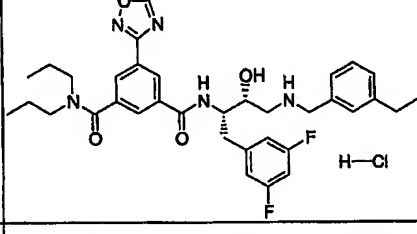
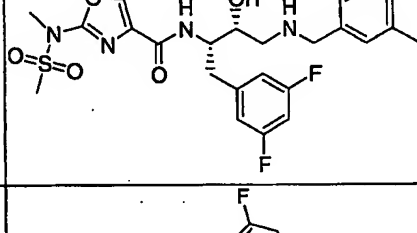
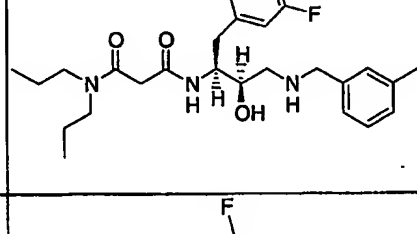
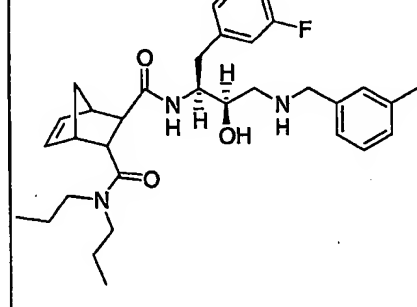
Step 1: A solution of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (25) (200 mg, 0.58 mmol),
 15 $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (16 mg, 0.03 mol %) and CuI (6 mg, 0.05 mol %) in triethylamine (1.2 mL) was heated to reflux. (Trimethylsilyl) acetylene (100 μL , 0.7 mmol) was added, and the bright yellow solution quickly turned orange then went brown within a minute. The reaction mixture was stirred for 3 h, cooled to
 20 room temperature, diluted with H_2O (20 mL), and extracted with CHCl_3 (3 x 15 mL). The combined organics were washed with

saturated NaCl (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give methyl 3-[(dipropylamino)carbonyl]-5-[(trimethylsilyl)ethynyl]benzoate 26 (185.5 mg): ^1H NMR (300 MHz, CDCl_3): δ 7.95 (s, 1H), 7.75 (s, 1H), 7.43 (s, 1H), 3.74 (s, 3H), 3.25 (br s, 2H), 2.95 (br s, 2H), 1.49 (br s, 2H), 1.34 (br s, 2H), 0.79 (br s, 3H), 0.56 (br s, 3H), 0.06 (s, 9H).

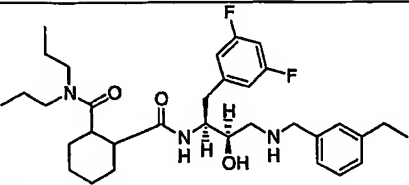
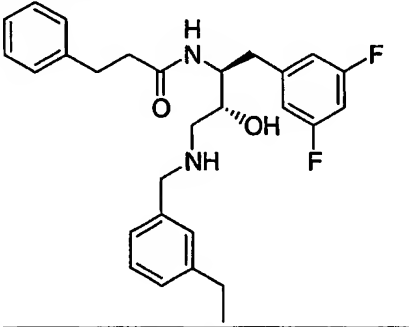
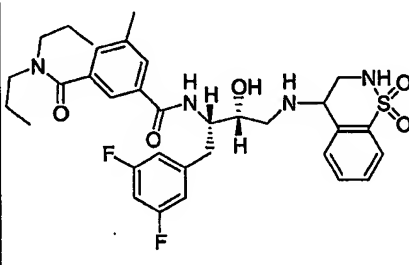
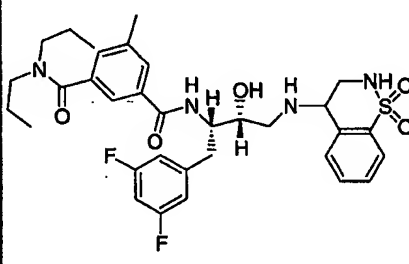
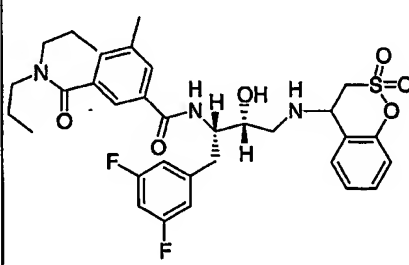
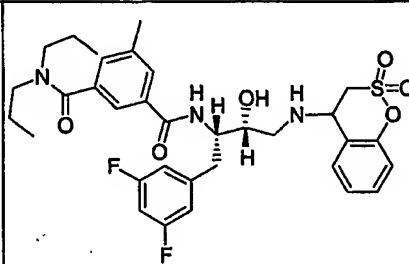
Step 2: To a stirred solution of methyl 3-[(dipropylamino)carbonyl]-5-[(trimethylsilyl)ethynyl]benzoate 26 (185.3 mg, 0.49 mmol) in MeOH (2.5 mL) was added a solution of KOH (2.9 mL of a 1 M solution in H_2O , 2.9 mmol). The resulting homogeneous brown solution turned to a white/brown suspension, then to a clear brown solution. The reaction mixture was stirred for 4 h, diluted with CHCl_3 (40 mL), separated and the organic layer was concentrated under reduced pressure to provide 3-[(dipropylamino)carbonyl]-5-ethynylbenzoic acid 27 (141.8 mg): ^1H NMR (300 MHz, CDCl_3): δ 8.22 (d, $J = 1$ Hz, 1H), 8.05 (d, $J = 1$ Hz, 1H), 7.71 (d, $J = 1$ Hz, 1H), 3.48 (br s, 2H), 3.17 (s, 1H), 3.16 (br s, 2H), 1.71 (d, $J = 7$ Hz, 2H), 1.55 (d, $J = 7$ Hz, 2H), 1.00 (d, $J = 7$ Hz, 3H), 0.78 (d, $J = 7$ Hz, 3H).

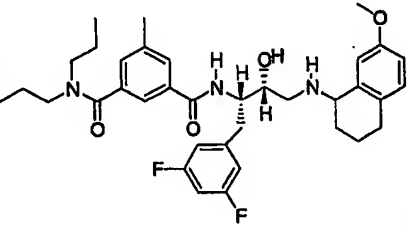
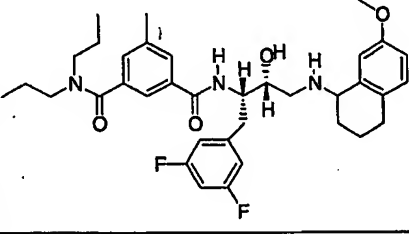
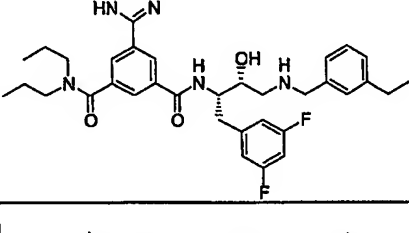
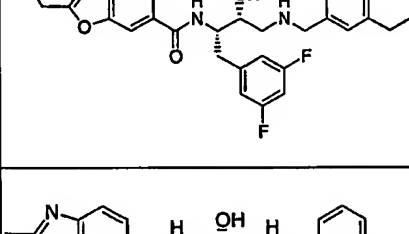
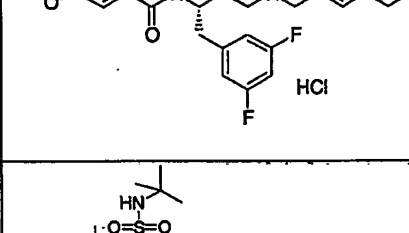
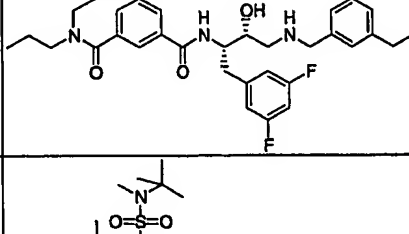
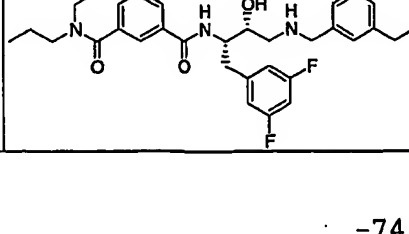
The following compounds were also prepared using the procedures described above and the schemes described below.

EXAMPLE	Structure	Compound Name(s)	Mass Spec
2999		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((2-hydroxyethyl)(methylsulfonyl)amino)benzamide	*575.3
3000		5-bromo-N¹-((1S,2R)-1-(2,4-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N³,N³-dipropylisophthalamide	**644, 646
3001		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((2-methoxyethyl)(methylsulfonyl)amino)benzamide hydrochloride	**590
3002		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((methylsulfonyl)methyl)benzamide	**531
3003		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-((4-hydroxybutyl)sulfonyl)-N³,N³-dipropylisophthalamide hydrochloride	**702
3004		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-(dipropylamino)isoquinoline-7-carboxamide	**589.4

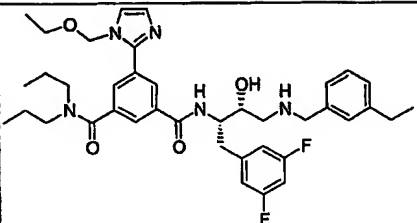
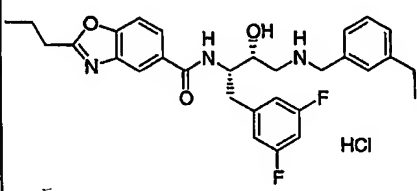
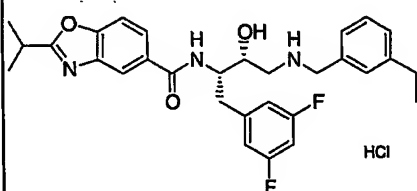
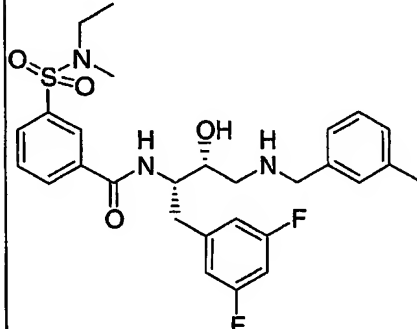
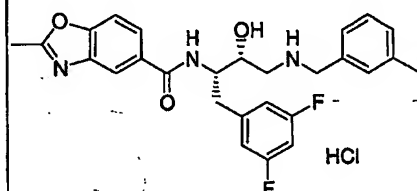
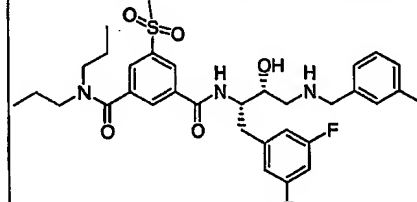
3005		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(2-hydroxyethyl)(methyl)amino]sulfonyl)-N³,N³-dipropylisophthalamide	**703
3006		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(ethylamino)sulfonyl]-N³,N³-dipropylisophthalamide	**673
3007		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(5-methyl-1,2,4-oxadiazol-3-yl)-N³,N³-dipropylisophthalamide hydrochloride	**648.4
3008		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	**** 537.3 (+)
3009		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³,N³-dipropylmalonamide	
3010		N²-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³,N³-dipropylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide	

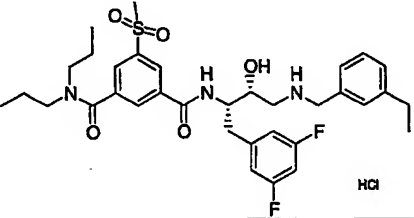
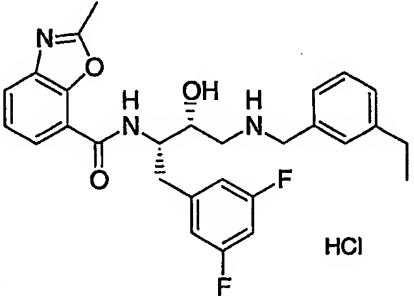
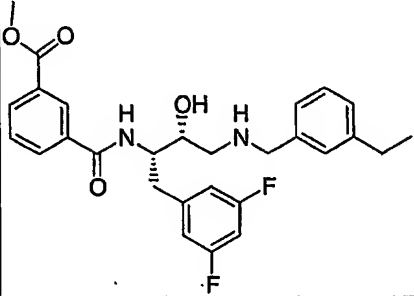
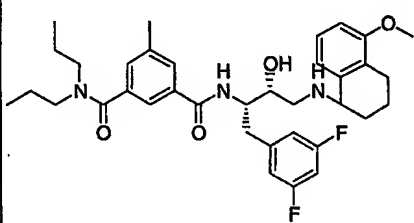
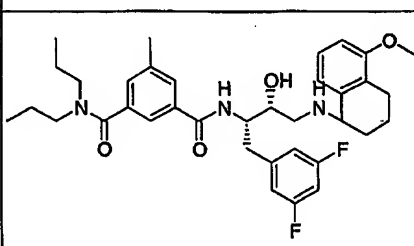
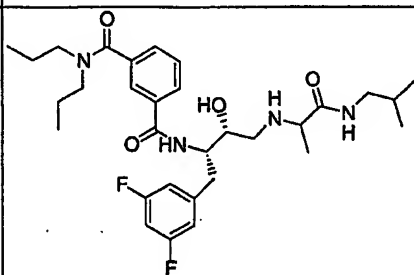
3011		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³,N³-dipropylcyclopentane-1,3-dicarboxamide	
3012		N²-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dimethyl-N⁵,N⁵-dipropylthieno[2,3-b]thiophene-2,5-dicarboxamide	
3013		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenyl-N⁵,N⁵-dipropylpentanediamide	
3014		N²-benzyl-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[2-(dipropylamino)-2-oxoethyl]glycinamide	
3015		3-(4-chlorophenyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁵,N⁵-dipropylpentanediamide	
3016		(2E)-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(methoxyimino)-N¹,N¹-dipropylpentanediamide	
3017		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[2-(dipropylamino)-2-oxoethyl]-N²-phenylglycinamide	

3018		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ² ,N ² -dipropylcyclohexane-1,2-dicarboxamide	
3019		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-phenylpropanamide	***467. 3
3020		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	
3021		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	
3022		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	
3023		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	

3024		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino)propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3025		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino)propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3026		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-(1H-imidazol-2-yl)-N³,N³-dipropylisophthalamide	**632.3
3027		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-propyl-1,3-benzoxazole-6-carboxamide	**522
3028		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-methyl-1,3-benzoxazole-6-carboxamide hydrochloride	**494
3029		5-((tert-butylamino)sulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N³,N³-dipropylisophthalamide	**701
3030		5-((tert-butyl(methyl)amino)sulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N³,N³-dipropylisophthalamide	**715

3031		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-isopropyl-1,3-benzoxazole-6-carboxamide	**522
3032		(2S)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-2-(1-naphthyl)ethanamide	
3033		(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-2-(1-naphthyl)ethanamide	
3034		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide	
3035		N¹-((1S,2R)-1-benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³-methyl-5-(1,3-oxazol-2-yl)-N³-propylisophthalamide	**569.3
3036			**642.3
3037			**614.4

3038		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]-N³,N³-dipropylisophthalamide	**690.3
3039		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-propyl-1,3-benzoxazole-5-carboxamide hydrochloride	**522
3040		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-isopropyl-1,3-benzoxazole-5-carboxamide hydrochloride	**522
3041		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[ethyl(methyl)amino]sulfonyl]benzamide	**560
3042		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-1,3-benzoxazole-5-carboxamide hydrochloride	**494
3043		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(methylsulfonyl)-N³,N³-dipropylisophthalamide	**644

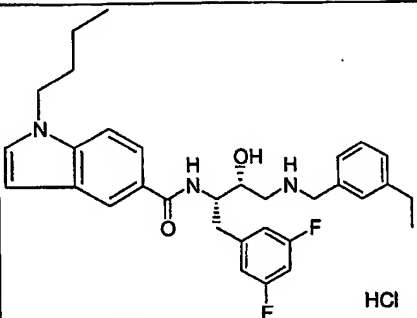
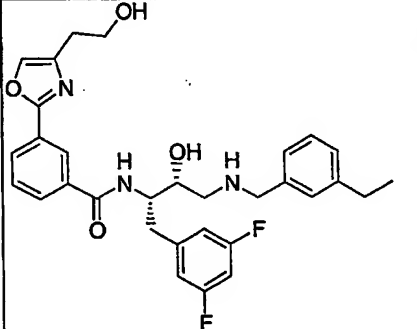
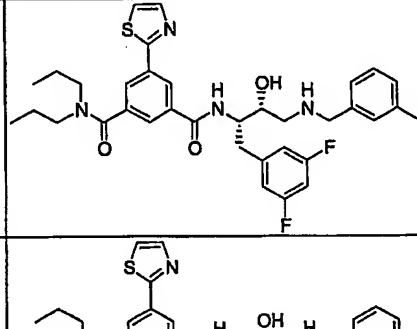
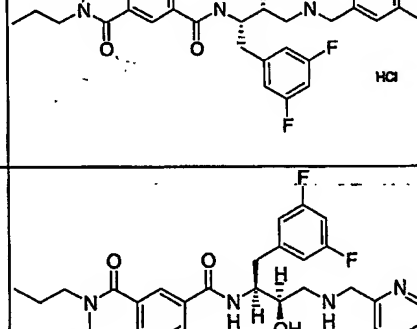
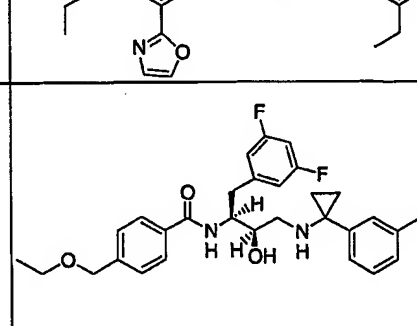
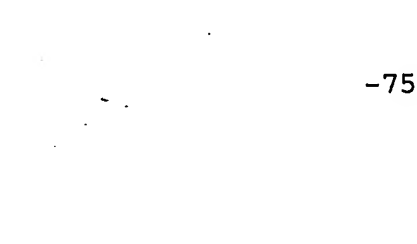
3044		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(methylsulfonyl)-N³,N³-dipropylisophthalamide hydrochloride	**645.04
3045		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-1,3-benzoxazole-7-carboxamide hydrochloride	**494
3046		methyl 3-(((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonylbenzoate	**497.3
3047		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3048		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3049		ELAN-91970	

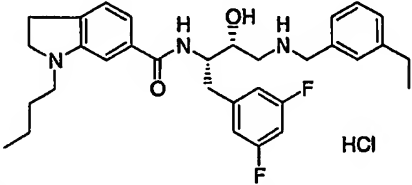
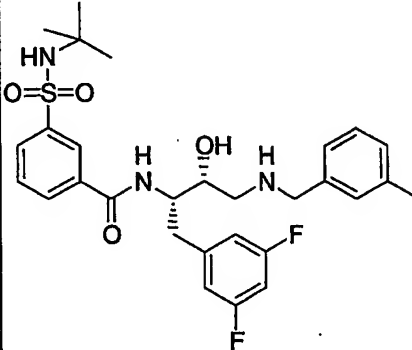
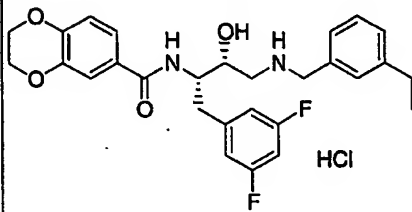
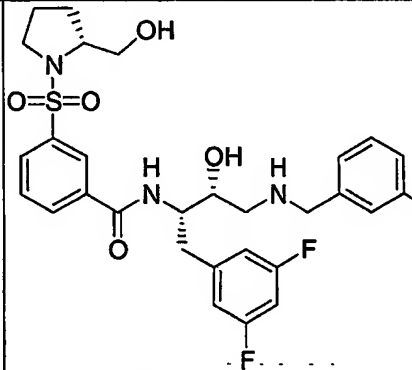
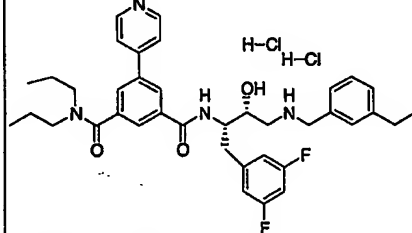
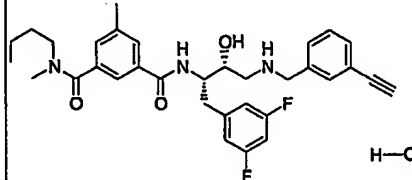
3050		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3051		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1S)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3052		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²,N²-dipropylcyclohexane-1,2-dicarboxamide	
3053		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl]benzamide	**616
3054		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[ethyl(methyl)amino]sulfonyl]benzamide	**560
3055		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[ethyl(methyl)amino]sulfonyl]benzamide (1:1)	***560.1

3056		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,5-dimethylbenzamide	
3057		N¹-butyl-N³-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-N¹-methyl-5-(1,3-thiazol-2-yl)isophthalamide	
3058		N¹-butyl-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N¹-methylpentanediamide	
3059		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁵,N⁵-dipropylpentanediamide	
3060		(2R)-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-N¹,N¹-dipropylpentanediamide	
3061		(2S)-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-N¹,N¹-dipropylpentanediamide	
3062		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁴,N⁴-dipropylsuccinamide	
3063		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[2-(dipropylamino)-2-oxoethyl]-N²-methylglycinamide	

3064		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[2-(dipropylamino)-2-oxoethyl]glycinamide	
3065		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-5-oxopentanamide	
3066		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁵-(2-furylmethyl)-N⁵-methylpentanediamide	
3067		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[4-(4-ethylpyridin-2-yl)methyl]amino]-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3068		N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-6-methyl-N²,N²-dipropylpyridine-2,4-dicarboxamide	
3069		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,2-dimethylchromane-7-carboxamide hydrochloride	**523
3070		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,2-dimethylchromane-6-carboxamide	**523

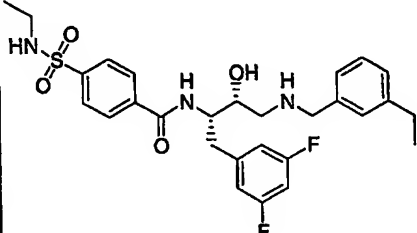
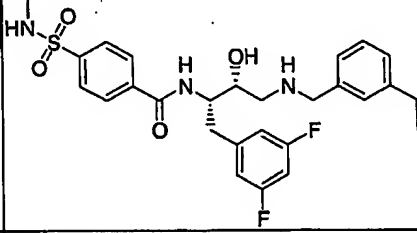
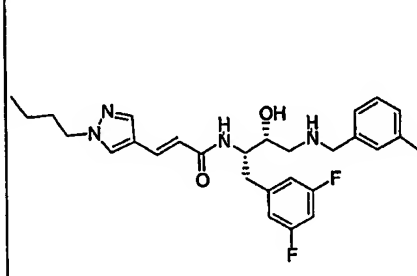
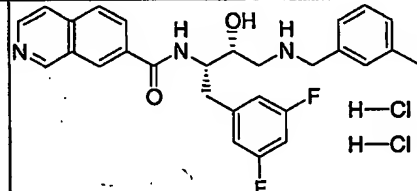
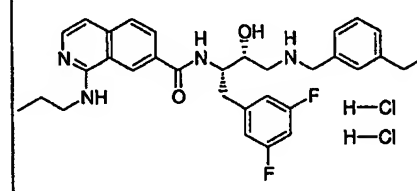
3071		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-1,3-benzoxazole-4-carboxamide hydrochloride	**494
3072		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-propyl-1,3-benzoxazole-4-carboxamide hydrochloride	
3073		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-((2R)-2-(methoxymethyl)pyrrolidin-1-yl)sulfonylbenzamide	**616
3074		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-((dihydroxy(2S)-2-(hydroxymethyl)pyrrolidin-1-yl)-lambda^4-sulfanyl)benzamide	**602
3075		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-6-carboxamide	**534
3076		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-propyl-1H-indole-6-carboxamide	**520

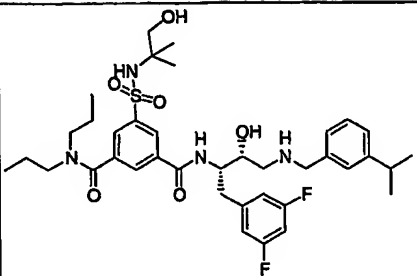
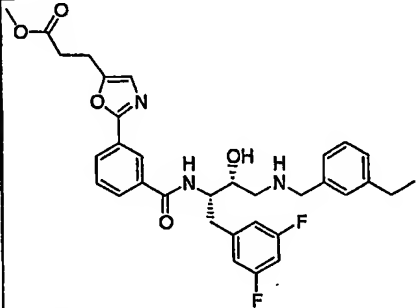
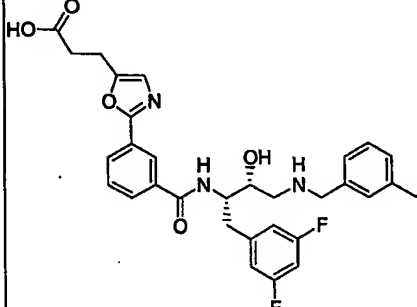
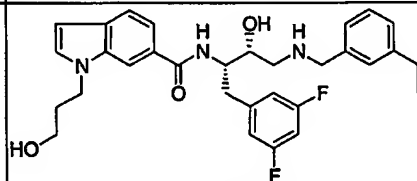
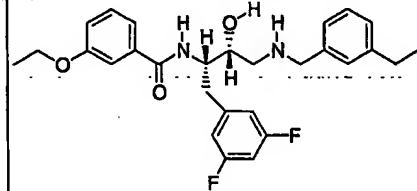
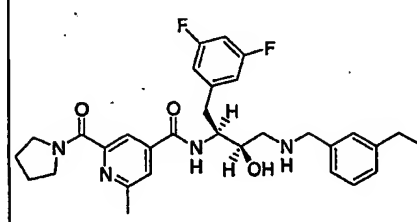
3077		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indole-5-carboxamide hydrochloride	**534
3078		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-[4-(2-hydroxyethyl)-1,3-oxazol-2-yl]benzamide	**550.3
3079		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-isopropylbenzyl)amino)propyl)-N³,N³-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	**663.3
3080		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-isopropylbenzyl)amino)propyl)-N³,N³-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide hydrochloride	**663.3
3081		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((4-ethylpyridin-2-yl)methyl)amino)-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3082		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((1-(3-ethynylphenyl)cyclopropyl)amino)-2-hydroxypropyl)-4-(ethoxymethyl)benzamide	

3083		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)indoline-6-carboxamide hydrochloride	**535.9
3084		3-[(tert-butylamino)sulfonyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	**574
3085		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,3-dihydro-1,4-benzodioxine-6-carboxamide hydrochloride	
3086		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl]benzamide	**602
3087		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³,N³-dipropyl-5-pyridin-4-ylisophthalamide dihydrochloride	**643.3
3088		N¹-butyl-N³-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl)-N¹,5-dimethylisophthalamide hydrochloride	*561

3089		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-isopropylbenzyl)amino)propyl)-3-(((2R)-2-(methoxymethyl)pyrrolidin-1-yl)carbonyl)-5-methylbenzamide hydrochloride	**608.3
3090		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethynylbenzyl)amino)-2-hydroxypropyl)-3-(((2R)-2-(methoxymethyl)pyrrolidin-1-yl)carbonyl)-5-methylbenzamide hydrochloride	**590.3
3091		3-(1-butyl-1H-pyrazol-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)propanamide	
3092		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((1-(3-ethylphenyl)cyclopropyl)amino)-2-hydroxypropyl)-3-(((2R)-2-(methoxymethyl)pyrrolidin-1-yl)carbonyl)-5-methylbenzamide hydrochloride	**620.3
3093		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indazole-6-carboxamide	
3094		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-thien-2-yl-1,3-thiazole-4-carboxamide	**** 528.2 (+)
3095		5-(aminosulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-methyl-1H-pyrrole-2-carboxamide	**** 521.2 (+)

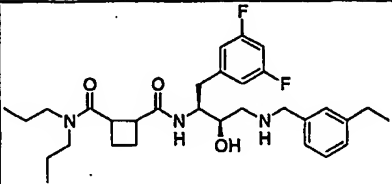
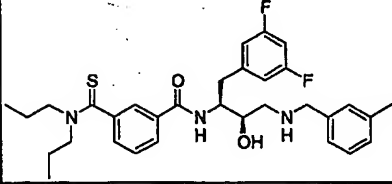
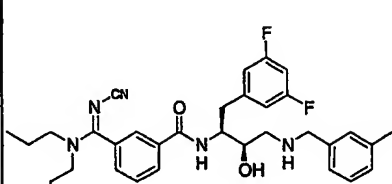
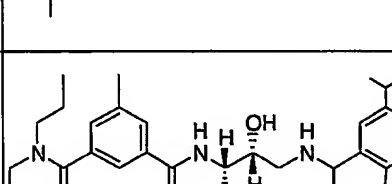
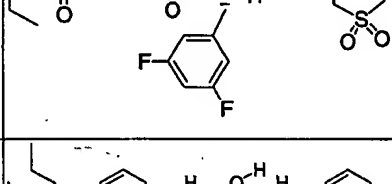
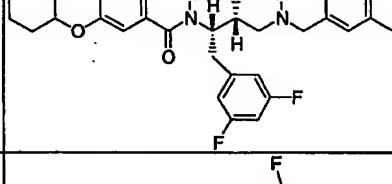
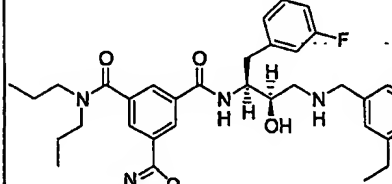
3096		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2-furylmethyl)sulfonylmethyl]-1,3-thiazole-4-carboxamide	**** 604.1 (+)
3097		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(4-fluorobenzyl)sulfonylmethyl]-1,3-thiazole-4-carboxamide	
3098		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide	**640.8
3099		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethynylphenyl)cyclopropyl)amino]-2-hydroxypropyl)-4-(2-methoxyethyl)benzamide	
3100		N¹-butyl-N³-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-phenylcyclopropyl)amino]propyl)-N¹-methyl-5-(1,3-thiazol-2-yl)isophthalamide	
3101		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-phenylcyclopropyl)amino]propyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	

3102		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(ethylamino)sulfonyl]benzamide	**546
3103		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(methylamino)sulfonyl]benzamide	**532
3104		(2E)-3-(1-butyl-1H-pyrazol-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)prop-2-enamide or (2E)-3-(1-butyl-1H-pyrazol-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)prop-2-enamide	
3105		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isoquinoline-7-carboxamide dihydrochloride	**490.1
3106		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(propylamino)isoquinoline-7-carboxamide dihydrochloride or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(propylamino)isoquinoline-7-carboxamide dihydrochloride	**547.3

3107		N-((1S,2R)-1-((3,5-difluorobenzyl)-2-hydroxy-3-((3-isopropylbenzyl)amino)propyl)-5-((2-hydroxy-1,1-dimethylethyl)amino)sulfonyl)-N,N'-dipropylisophthalamide	**730.8
3108		methyl 3-(2-((3-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl)phenyl)-1,3-oxazol-5-yl)propanoate	**591.9
3109		3-(2-((3-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl)phenyl)-1,3-oxazol-5-yl)propanoic acid	**578.2
3110		N-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-((3-hydroxypropyl)-1H-indole-6-carboxamide	**536.8
3111		N-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-ethoxybenzamide	
3112		N-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-methyl-6-(pyrrolidin-1-ylcarbonyl)isonicotinamide	

3113		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[[6-ethylpyridin-2-yl)methyl]amino]-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3114		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(dipropylamino)sulfonyl]benzamide	
3115		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[[6-ethylpyridin-2-yl)methyl]amino]-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3116		tert-butyl (1R)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino]carbonyl]-3-(methylsulfinyl)propyl carbamate	**** 582.1 (+)
3117		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide or ELAN154894	
3118		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide hydrochloride	**539.3
3119		(2R)-2-amino-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(methylsulfinyl)butanamide	**** 482.2 (+)

3120		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-([ethyl(methyl)amino]sulfonyl)-5-((2S)-2-(methoxymethyl)pyrrolidin-1-yl)carbonyl)benzamide	**701
3121		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-([methyl(propyl)amino]isoquinoline-7-carboxamide or N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-([methyl(propyl)amino]isoquinoline-7-carboxamide	**561.4
3122		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(1,3-oxazol-2-yl)benzamide	**506.2
3123		N ¹ -[(1S,2R)-3-([1-(3-bromophenyl)cyclopropyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N ³ ,N ³ -dipropylisophthalamide	
3124		N ¹ -[(1S,2R)-3-([1-(3-bromophenyl)cyclopropyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N ³ ,N ³ -dipropylisophthalamide hydrochloride	**709.2 + 711.2
3125		N ³ -[(1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl]-N ³ ,N ³ -dipropyl-1H-pyrazole-3,5-dicarboxamide	

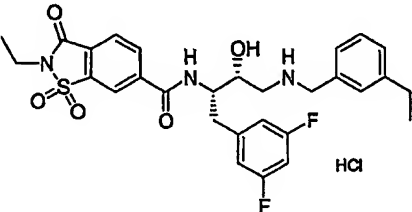
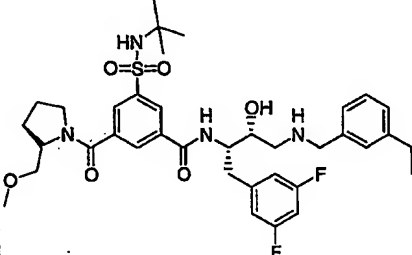
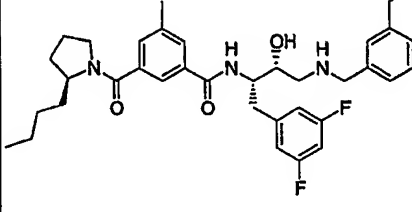
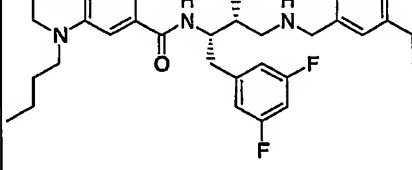
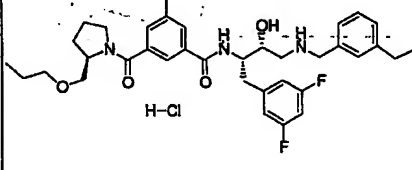
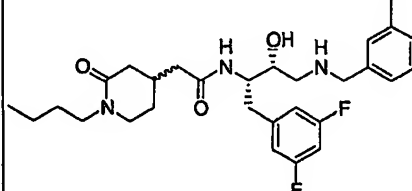
3126		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^2,N^2 -dipropylcyclobutane-1,2-dicarboxamide	
3127		N -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(dipropylamino)carbonothioyl]benzamide	
3128		3-[(E)-(cyanoimino)(dipropylamino)methyl]- N -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide	
3129		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide	
3130		N -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1-propylbutoxy)benzamide	
3131		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[5-ethylpyridin-3-yl)methyl]amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)- N^3,N^3 -dipropylisophthalamide	
3132		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide	

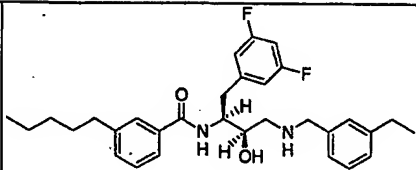
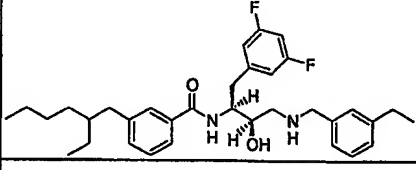
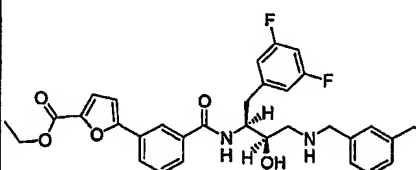
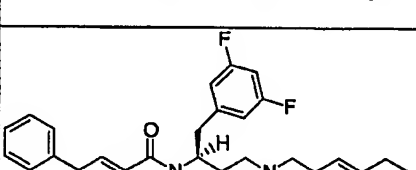
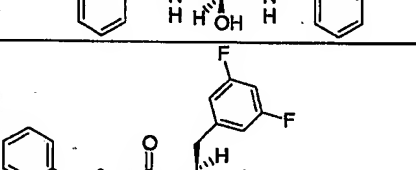
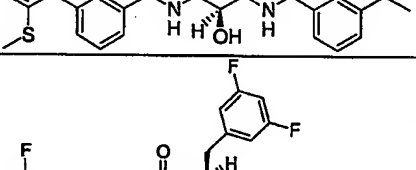
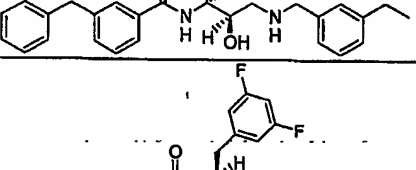
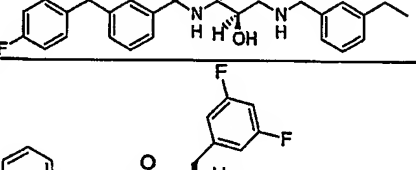
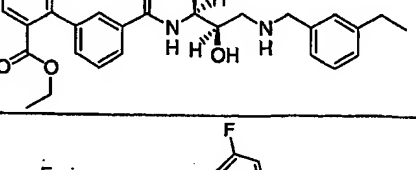
3133		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(2-methoxyethyl)-1H-indole-6-carboxamide	**536
3134		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide hydrochloride	**496
3135		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-[[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl]benzamide	**757
3136		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-thiazol-2-yl)benzamide	**522.2
3137		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,8-diethoxyquinoline-2-carboxamide	****. 578.3 (+)
3138		2-(4-butyl-3-oxopiperazin-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide dihydrochloride	
3139		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³-[2-(dimethylamino)ethyl]-N³,5-dimethylisophthalamide	

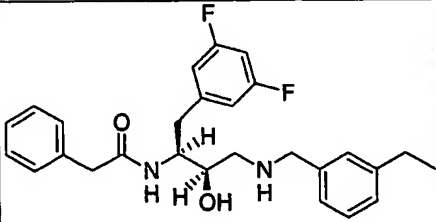
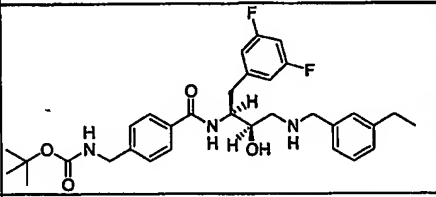
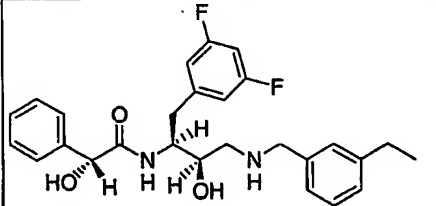
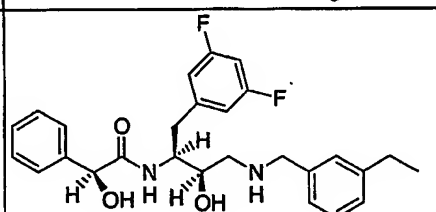
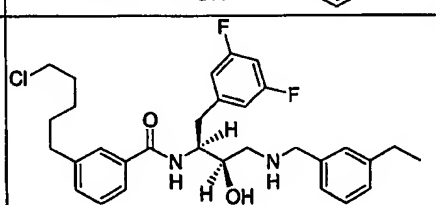
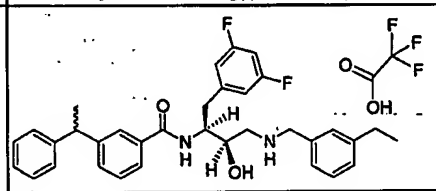
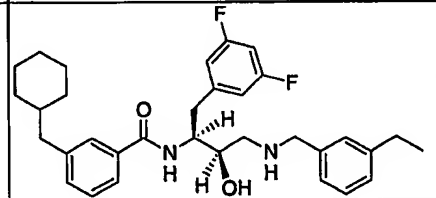
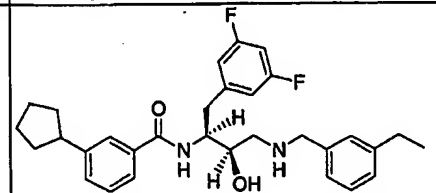
3140		N¹-((1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methylbutandyl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide
3141		N¹-((1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methylpentanoyl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide
3142		isobutyl (2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutylcarbamate
3143		ethyl (2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutylcarbamate
3144		N¹-((1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(pyrimidin-2-ylamino)propyl)-5-methyl-N³,N³-dipropylisophthalamide
3145		N¹-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-N³-[(1S)-1-methylpropyl]isophthalamide
3146		N¹-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-N³-[(1R)-1-methylpropyl]isophthalamide

3147		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide	**554.4
3148		1-[(butyl(methyl)amino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isoquinoline-7-carboxamide or 1-[(butyl(methyl)amino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isoquinoline-7-carboxamide	**575.4
3149		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,3-dihydro-2-benzothiophene-5-carboxamide 2,2-dioxide hydrochloride	**529
3150		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-3-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl)-5-methylbenzamide	
3151		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-3-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl)-5-methylbenzamide trifluoroacetate	
3152		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-isobutyl-1H-indole-6-carboxamide	**534.2

		carboxamide	
3153		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1H-indole-6-carboxamide	**627.8 6
3154		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-methyl-1H-indole-6-carboxamide	**548.9 4
3155		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-oxo-2-propyl-2,3-dihydro-1,2-benzisothiazole-6-carboxamide 1,1-dioxide hydrochloride	**586
3156		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide	**601.9 9
3157		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(diethylamino)-6-methylisonicotinamide	**553
3158		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylsulfonyl)methyl)-1,3-thiazole-4-carboxamide	**** (537.8) (+)
3159		4-amino-1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indole-6-carboxamide hydrochloride	

3160		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-ethyl-3-oxo-2,3-dihydro-1,2-benzisothiazole-6-carboxamide 1,1-dioxide hydrochloride	
3161		3-((tert-butylamino)sulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-(((2S)-2-(methoxymethyl)pyrrolidin-1-yl)carbonyl)benzamide	
3162		3-(((2S)-2-butylpyrrolidin-1-yl)carbonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-methylbenzamide	
3163		4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide	
3164		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-methyl-5-(((2R)-2-(propoxymethyl)pyrrolidin-1-yl)carbonyl)benzamide hydrochloride	
3165		2-(1-butyl-2-oxopiperidin-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)acetamide	

3166		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-pentylbenzamide	
3167		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-ethylhexyl)benzamide	
3168		ethyl 5-{3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino]carbonyl}phenyl-2-furoate	
3169		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,1'-biphenyl-3-carboxamide	
3170		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2'-(methylthio)-1,1'-biphenyl-3-carboxamide	
3171		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-fluorobenzyl)benzamide	
3172		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4-fluorobenzyl)benzamide	
3173		ethyl 3'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino]carbonyl-1,1'-biphenyl-2-carboxylate	
3174		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3',5'-difluoro-1,1'-biphenyl-3-carboxamide	

3175		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylacetamide	
3176		tert-butyl 4-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]benzylcarbamate	
3177		(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylethanamide	
3178		(2S)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylethanamide	
3179		3-(5-chloropentyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	
3180		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(1-phenylethyl)benzamide trifluoroacetate	
3181		3-(cyclohexylmethyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	
3182		3-cyclopentyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	

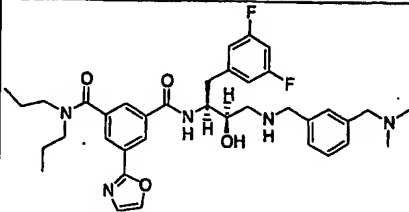
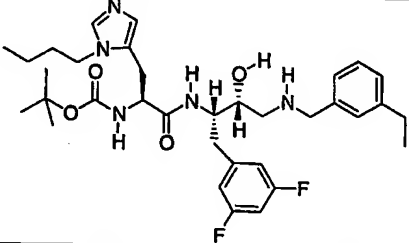
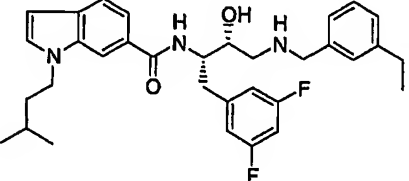
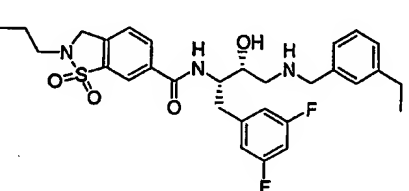
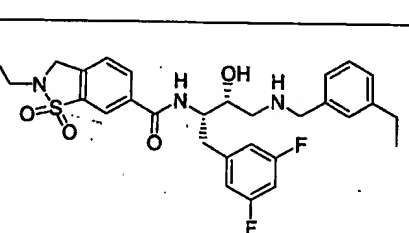
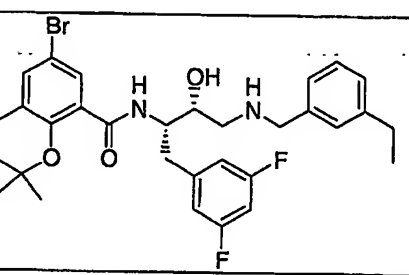
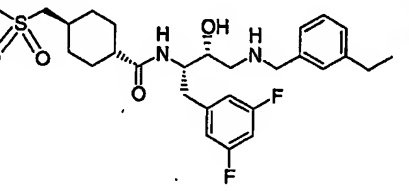
3183		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hex-5-enylbenzamide	
3184		3-(6-cyanoethyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	
3185		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(2-formylthien-3-yl)benzyl)amino]-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3186		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(5-formylthien-3-yl)benzyl)amino]-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3187		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(6-methoxypyridin-2-yl)benzyl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3188		N¹-((1S,2R)-3-[(3-(5-cyanopyridin-3-yl)benzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3189		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(6-fluoropyridin-3-yl)benzyl)amino]-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3190		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyrimidin-4-ylbenzyl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide	

3191		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(5-ethylpyrimidin-2-yl)benzyl]amino)-2-hydroxypropyl)-5-methyl-N³,N³-dipropylisophthalamide	
3192		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(5-ethylpyrimidin-2-yl)benzyl]amino)propyl)-5-methyl-N³,N³-dipropylisophthalamide	
3193		methyl 2-(((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(5-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl)-6-methylisonicotinate	
3194		N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(5-ethylbenzyl)amino]-2-hydroxypropyl)-6-methyl-N²,N²-dipropylpyridine-2,4-dicarboxamide 1-oxide	
3195		1-butyl-4-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(5-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-6-carboxamide	
3196		1-butyl-4-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(5-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-6-carboxamide hydrochloride	
3197		5-(diethylamino)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(5-ethylbenzyl)amino]-2-hydroxypropyl)-N³,N³-dipropylisophthalamide	

3198		N¹-[(1S,2R)-3-[[3-(diethylamino)benzyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3199		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-(dimethylamino)-N³,N³-dipropylisophthalamide	
3200		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[2-(2-ethylpyridin-4-yl)methyl]amino]-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3201		N²-(tert-butoxycarbonyl)-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-L-norleucinamide	
3202		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)methyl]benzamide	
3203		N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-3-[(2-hydroxyethyl)(propyl)amino]methyl)-5-methylbenzamide dihydrochloride	
3204		N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-3-[(ethyl(propyl)amino)methyl]-5-methylbenzamide dihydrochloride	

3205		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1,3-dihydro-2,1-benzisothiazole-5-carboxamide 2,2-dioxide	
3206		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-L-norleucinamide	
3207		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(dimethylamino)benzyl)amino]-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3208		2-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methylisonicotinamide	
3209		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-3-[(2-hydroxyethyl)(propyl)amino]methylbenzamide dihydrochloride	
3210		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-fluoro-4-propoxyphenyl)acetamide	
3211		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-methoxy-4-propoxyphenyl)acetamide	

3212		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-3-methyl-5-([methyl(propyl)amino]methyl)benzamide dihydrochloride	
3213		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-3-[(dipropylamino)methyl]-5-methylbenzamide dihydrochloride	
3214		3-([butyl(methyl)amino]methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-5-methylbenzamide hydrochloride	
3215		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(piperidin-1-ylsulfonyl)benzamide	
3216		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino)propyl)-3-methylbenzamide	
3217		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-4-(3-methoxypropyl)benzamide	
3218		5-amino-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N³,N³-dipropylisophthalamide	

3219		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({3-[(dimethylamino)methyl]benzyl}amino)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3220		N-(tert-butoxycarbonyl)-3-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-L-histidinamide	
3221		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1-isopentyl-1H-indole-6-carboxamide	
3222		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-propyl-2,3-dihydro-1,2-benzisothiazole-6-carboxamide 1,1-dioxide	
3223		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-ethyl-2,3-dihydro-1,2-benzisothiazole-6-carboxamide 1,1-dioxide	
3224		6-bromo-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2,2-dimethylchromane-8-carboxamide	
3225		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[(methylsulfonyl)methyl]cyclohexanecarboxamide	

3226		N¹-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-piperidin-4-yl-N³,N³-dipropylisophthalamide	
3227		N-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-5-(1,3-oxazol-2-yl)benzamide hydrochloride	
3228		N-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(methylsulfonyl)methyl]thiophene-2-carboxamide	
3229		3-[(cyclohexylamino)methyl]-N-((1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-5-methylbenzamide hydrochloride	
3230		2-(2-chlorophenoxy)-N-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	
3231		N-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)pyrazine-2-carboxamide	

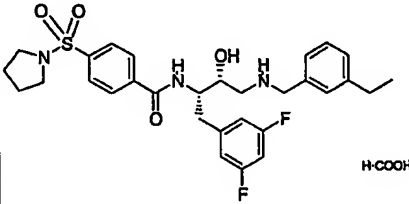
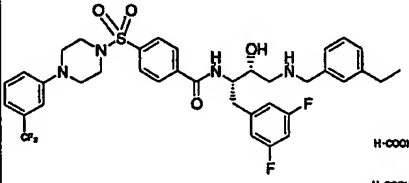
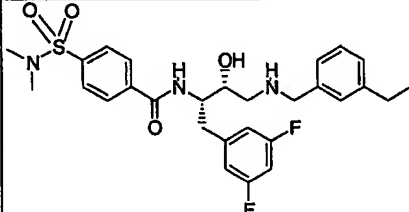
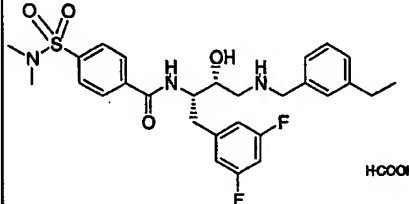
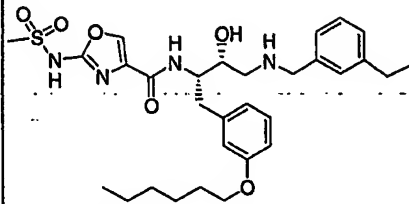
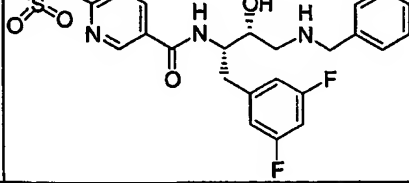
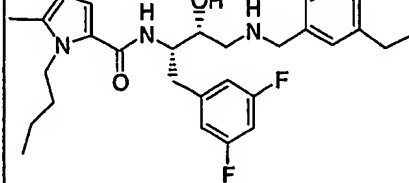
3232		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(phenylsulfonyl)propanamide
3233		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]-6-methylisonicotinamide
3234		3-(((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl)-5-methylbenzoic acid hydrochloride
3235		6-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,2-dimethylchromane-8-carboxamide
3236		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-5-(1,3-thiazol-2-yl)benzamide hydrochloride
3237		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(4-ethoxyphenyl)acetamide (1:1)

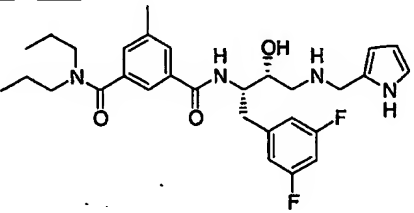
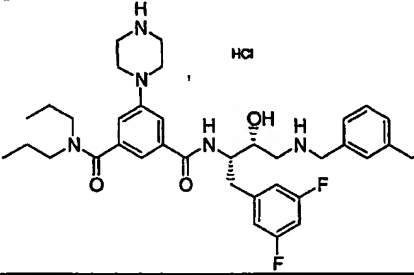
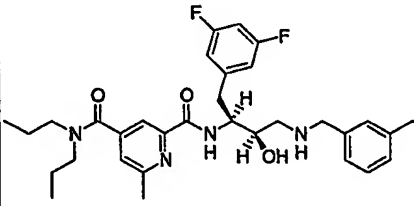
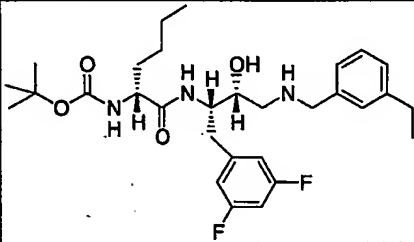
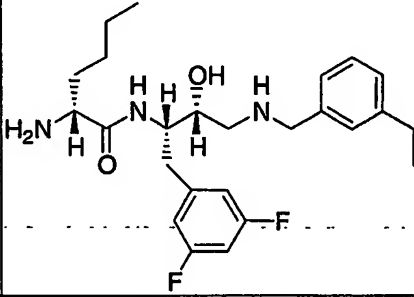
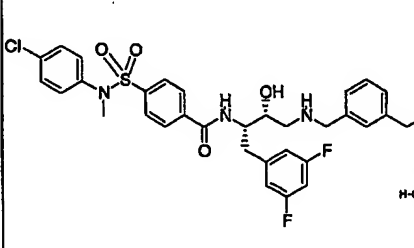
3238		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-5-[[(2S)-2-propylpyrrolidin-1-yl]carbonyl]benzamide (1:1)	
3239		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[(2R)-2-(2-methoxyethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide	
3240		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(methylsulfonyl)methyl]cyclohexanecarboxamide	
3241		3-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1H-indole-5-carboxamide	
3242		formic acid compound with 2-(1-butyl-2-oxo-1,2-dihydropyridin-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide (1:1)	
3243		3-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-L-histidinamide	
3244		5-[(diethylamino)methyl]-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³,N³-dipropylisophthalamide	

3245		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(dimethylamino)methyl]-N ³ ,N ³ -dipropylisophthalamide	
3246		N-((1S,2R)-3-[(3-ethylbenzyl)amino]-1-[3-(hexyloxy)benzyl]-2-hydroxypropyl)-3-(1,3-oxazol-2-yl)benzamide	**570.2
3247		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-hydroxy-4-methoxyphenyl)acetamide (1:1)	
3248		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-thiazolidin-3-ylsulfonyl)benzamide (1:1)	***589.9
3249		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzamide (1:1)	***634.0
3250		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(4-phenylpiperazin-1-yl)sulfonyl]benzamide	***663.0

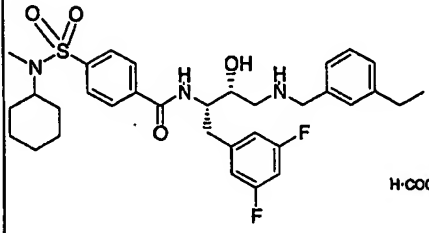
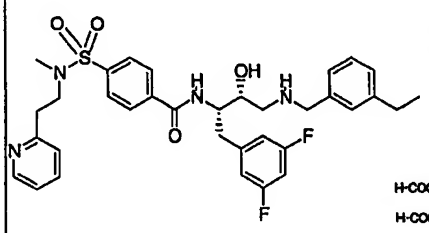
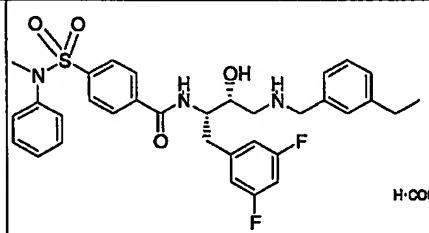
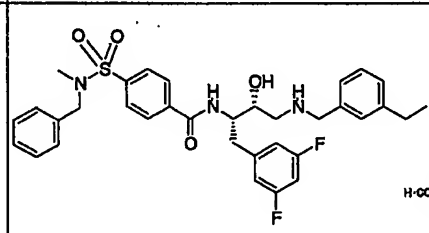
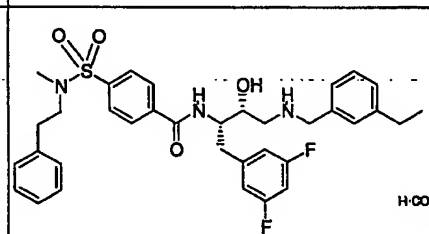
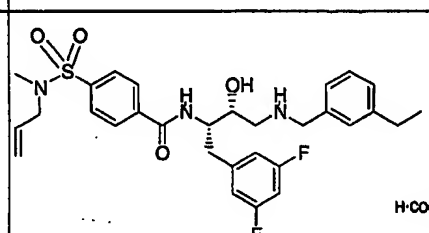
3251		3-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-5-carboxamide	
3253		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-1H-benzimidazole-6-carboxamide or ELAN155076	
3254		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(methylsulfonyl)methyl]nicotinamide	**532
3255		N¹-[(1S,2R)-3-({3-[(diethylamino)methyl]benzyl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3256		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetamide	
3257		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide	
3258		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-6-(1,3-oxazol-2-yl)isonicotinamide	

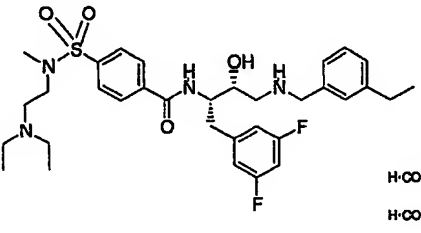
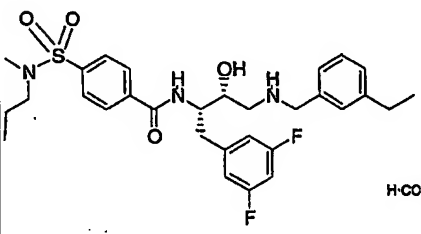
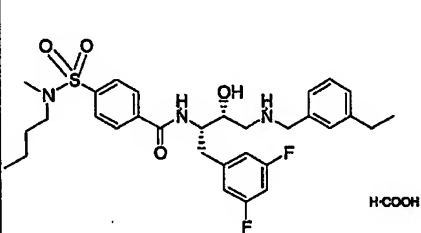
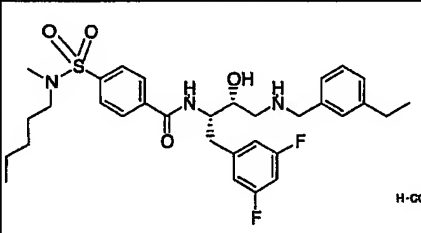
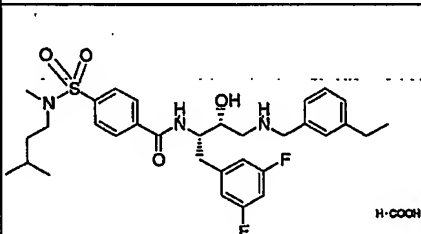
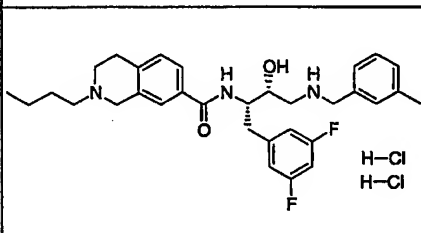
3259		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-1H-benzimidazole-5-carboxamide	
3260		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino)propyl)-3-methylbenzamide	
3261		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-piperidin-3-yl-N³,N³-dipropylisophthalamide hydrochloride	**649.6
3262		3-([benzyl(methyl)amino]methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-5-methylbenzamide dihydrochloride	**684.2
3263		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-((4-fluorophenyl)piperazin-1-yl)sulfonylbenzamide (2:1)	***680.9
3264		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-(pyrrolidin-1-ylsulfonyl)benzamide	****572

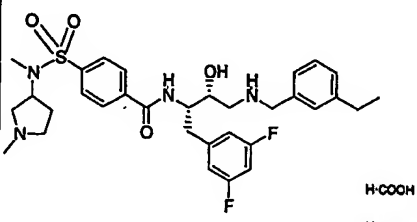
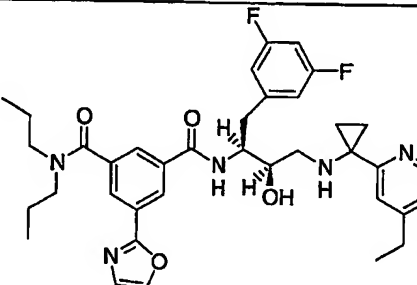
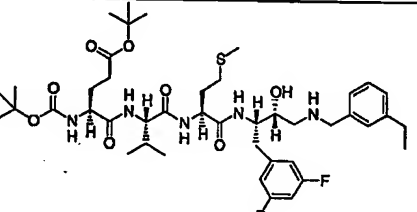
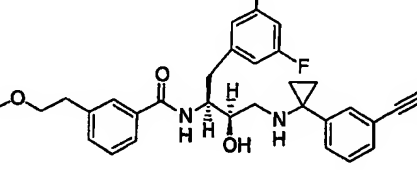
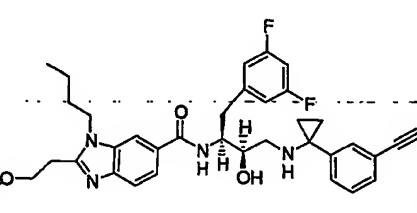
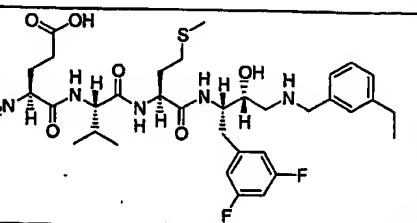
3265		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(pyrrolidin-1-ylsulfonyl)benzamide (1:1)	**** 572.0
3266		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[(4-[3-(trifluoromethyl)phenyl]piperazin-1-yl)sulfonyl]benzamide (2:1)	**** 731.0
3267		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[(dimethylamino)sulfonyl]benzamide	****546
3268		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[(dimethylamino)sulfonyl]benzamide (1:1)	**** 546.0
3269		N-[(1S,2R)-3-[(3-ethylbenzyl)amino]-1-[3-(hexyloxy)benzyl]-2-hydroxypropyl]-2-[(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	**587.5
3270		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-6-[(methylsulfonyl)methyl]nicotinamide	**532
3272		1-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methyl-1H-pyrrole-2-carboxamide	**498.4

3273		N¹-({(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-pyrrol-2-ylmethyl)amino]propyl}-5-methyl-N³,N³-dipropylisophthalamide	**541.2
3274		N¹-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperazin-1-yl-N³,N³-dipropylisophthalamide hydrochloride	**650.4
3276		N²-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-methyl-N⁴,N⁴-dipropylpyridine-2,4-dicarboxamide	
3277		N²-(tert-butoxycarbonyl)-N¹-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-norleucinamide	
3278		N¹-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-norleucinamide	
3281		formic acid compound with 4-[[[(4-chlorophenyl)(methyl)amino]sulfonyl]-N-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (1:1)	*** 642.0

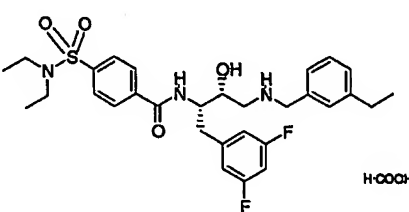
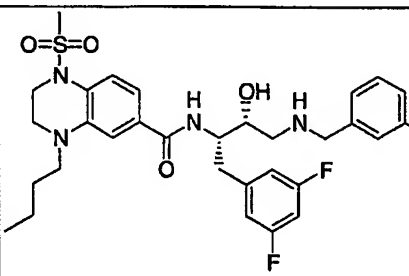
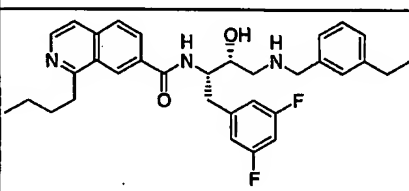
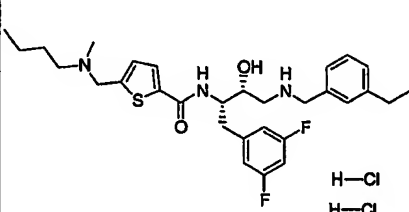
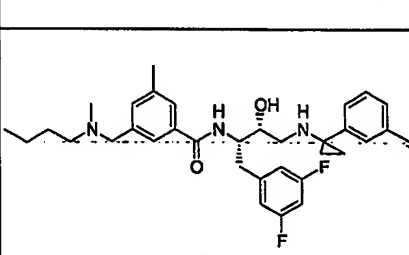
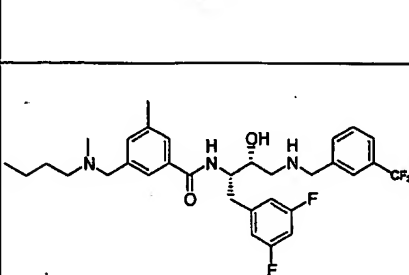
3282	 H-COOH	formic acid compound with 4- {[benzyl (phenyl) amino] sulfonyl}-N-{(1S,2R)- 1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}benzamid e (1:1)	*** 684.1
3283	 H-COOH	formic acid compound with N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-4- ylsulfonyl}benzamide (1:1)	***588. 1
3285		N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-2-(3- oxo-4- propylcyclohexyl)aceta mide	**515.4
3286		N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-2-(3- oxocyclohexyl)acetamid e	**473.3
3287		N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-1,1- dipropyl-3,4-dihydro- 1H-isochromene-7- carboxamide	**579.4
3288	 H-COOH	formic acid compound with 4-{{(2- cyanoethyl) (methyl) ami no]sulfonyl}-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}benzamid e (1:1)	***585 0

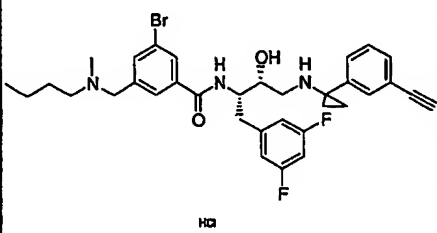
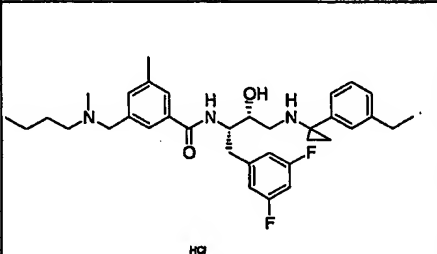
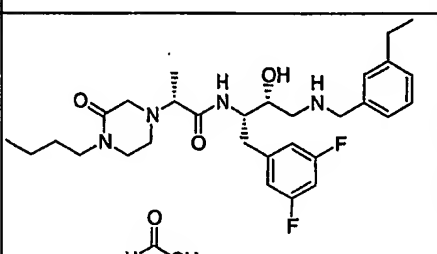
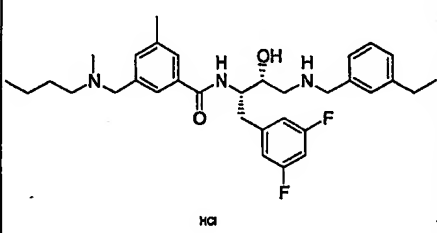
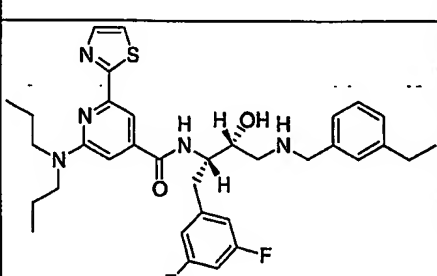
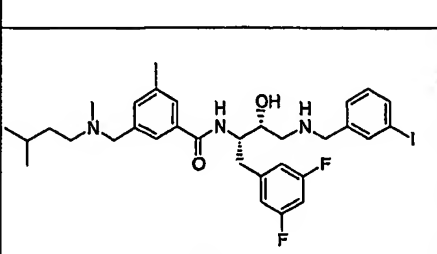
3289		formic acid compound with 4- {[cyclohexyl(methyl)amino]sulfonyl}-N- {(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (1:1)	***614. 0
3290		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-([methyl(2-pyridin-2-ylethyl)amino]sulfonyl)benzamide (2:1)	***637. 0
3291		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-([methyl(phenyl)amino]sulfonyl)benzamide (1:1)	***608. 1
3292		formic acid compound with 4- {[benzyl(methyl)amino]sulfonyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (1:1)	***622. 1
3293		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-([methyl(2-phenylethyl)amino]sulfonyl)benzamide (1:1)	***636. 1
3294		formic acid compound with 4- {[allyl(methyl)amino]sulfonyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (1:1)	***572. 1

3295		formic acid compound with 4-[[[2-(diethylamino)ethyl](methyl)amino]sulfonyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]benzamide (2:1)	***631.1
3296		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[[[methyl(propyl)amino]sulfonyl]benzamide (1:1)	***574.1
3297		formic acid compound with 4-[[[butyl(methyl)amino]sulfonyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]benzamide (1:1)	***588.1
3298		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[[[methyl(pentyl)amino]sulfonyl]benzamide (1:1)	***602.1
3299		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-[[[isopentyl(methyl)amino]sulfonyl]benzamide (1:1)	***602.1
3300		2-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1,2,3,4-tetrahydroisoquinoline-7-carboxamide dihydrochloride	**550.3

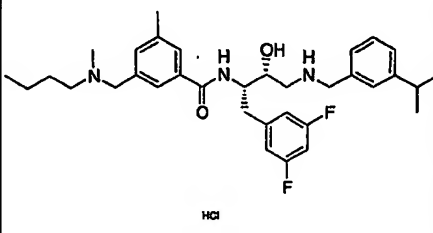
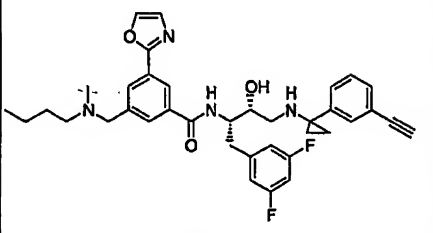
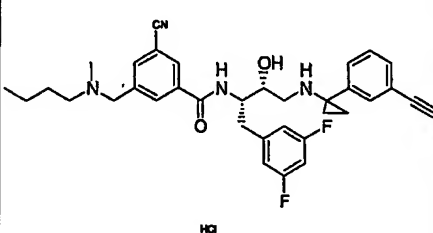
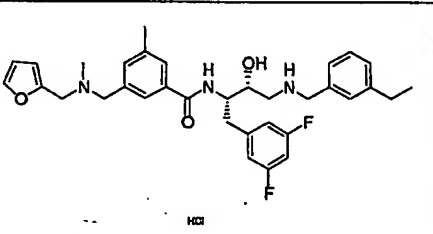
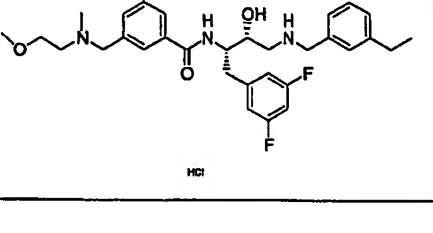
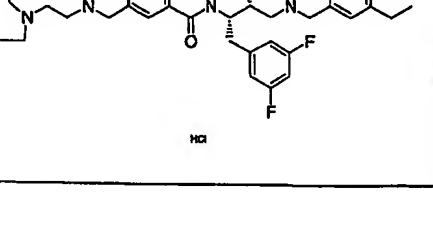
3301		formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[methyl(1-methylpyrrolidin-3-yl)amino]sulfonyl]benzamide (2:1)	***615. 0
3302		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(4-ethylpyridin-2-yl)cyclopropyl]amino]-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3303		ELAN-155957	
3304		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-2-(2-methoxyethyl)benzamide	
3305		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-2-(2-methoxyethyl)-1H-benzimidazole-6-carboxamide	
3306		L-alpha-glutamyl-L-valyl-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-L-methioninamide	

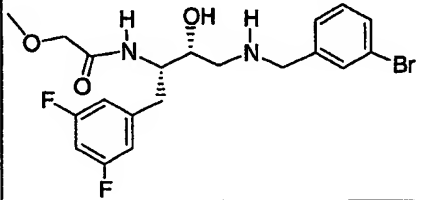
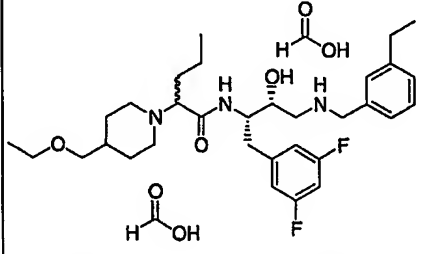
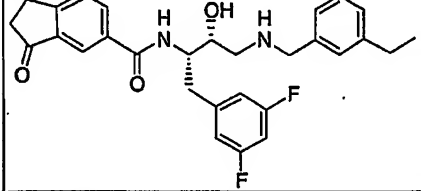
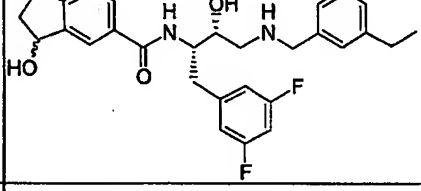
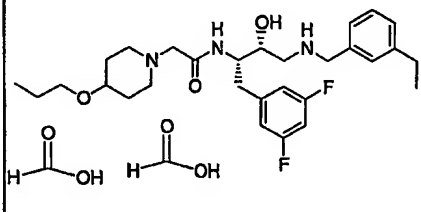
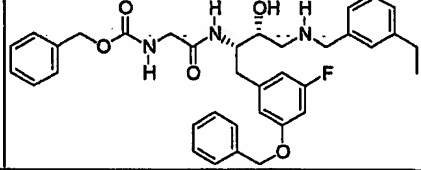
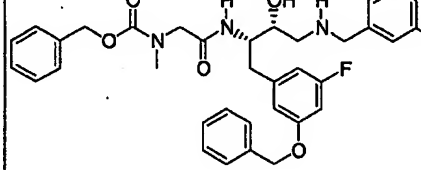
3307		3- ({[cyclohexyl(methyl)amino]methyl}-N- (1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(3- iodobenzyl)amino]propyl)-5-methylbenzamide hydrochloride	**676.2
3309		formic acid compound with 2-(4-butyl-2,5- dioxopiperazin-1-yl)- N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)acetamid e (1:1)	
3310		3-bicyclo[2.2.1]hept- 2-yl-N-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)benzamid e	
3311		3-(butylamino)-N- (1S,2R)-1-(3,5- difluorobenzyl)-3-([1- (3- ethynylphenyl)cyclopro pyl]amino)-2- hydroxypropyl)-4-(2- methoxyethyl)benzamide	
3312		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-([1- (3- ethynylphenyl)cyclopro pyl]amino)-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide	
3313		N-((1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-((1S)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino)propyl)-3- methylbenzamide	
3314		formic acid compound with N-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-4- (dipropylamino)sulfonyl	***602. 0

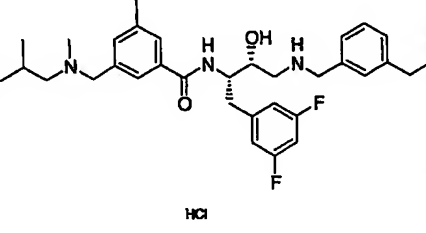
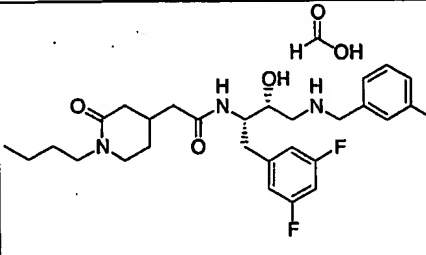
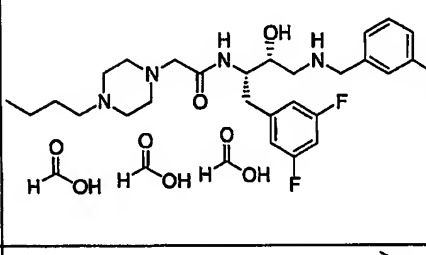
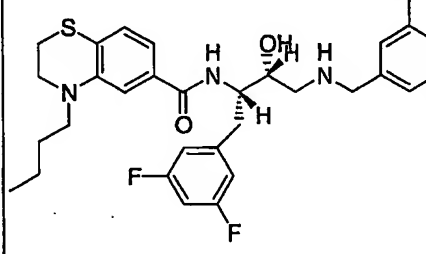
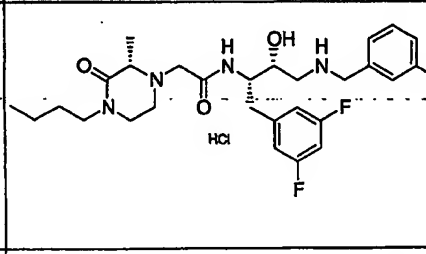
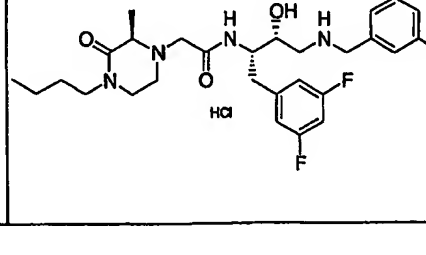
		[(dipropylamino)sulfonyl]benzamide (1:1)	
3315		formic acid compound with 4-[(diethylamino)sulfonyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide (1:1)	***574.0
3316		4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide	**629
3317		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isoquinoline-7-carboxamide	**546.3
3318		5-((butyl(methyl)amino)methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thiophene-2-carboxamide dihydrochloride	**544.3
3319		3-((butyl(methyl)amino)methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-5-methylbenzamide hydrochloride	**574.3
3320		3-((butyl(methyl)amino)methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((trifluoromethyl)benzyl)amino)propyl)-5-methylbenzamide hydrochloride	**592.3

3321		3-bromo-5- {[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)benzamide hydrochloride	**638.2
3322		3- {[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-5-methylbenzamide hydrochloride	**578.4
3323		(2R)-2-(4-butyl-3-oxopiperazin-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)propanamide	
3324		3- {[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-methylbenzamide hydrochloride	**552.3
3325		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(dipropylamino)-6-(1,3-thiazol-2-yl)isonicotinamide	
3326		N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-iodobenzyl)amino)propyl)-3-({[isopentyl(methyl)amino]methyl}-5-methylbenzamide hydrochloride	**664.2

3327		N-((1S,2R)-1-(3-butoxybenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	**559.1
3328		3-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)imidazo[1,2-a]pyridine-6-carboxamide	
3329		2-[butyl(methyl)amino]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-(1,3-oxazol-2-yl)isonicotinamide	
3330		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,3-benzodioxole-5-carboxamide	**483.2
3333		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[methyl(propyl)amino]-6-(1,3-oxazol-2-yl)isonicotinamide	
3334		3-([butyl(methyl)amino]methyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-phenylcyclopropyl)amino]propyl)-5-methylbenzamide hydrochloride	**550.3

3335		3- { [butyl (methyl) amino]m ethyl}-N-((1S,2R)-1- (3,5-difluorobenzyl)- 2-hydroxy-3-[(3- isopropylbenzyl) amino] propyl)-5- methylbenzamide hydrochloride	**566.3
3337		3- { [butyl (methyl) amino]m ethyl}-N-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[[1-(3- ethynylphenyl) cyclopro pyl] amino]-2- hydroxypropyl)-5-(1,3- oxazol-2-yl) benzamide hydrochloride	**627.3
3339		3- { [butyl (methyl) amino]m ethyl}-5-cyano-N- ((1S,2R)-1-(3,5- difluorobenzyl)-3-[[1- (3- ethynylphenyl) cyclopro pyl] amino]-2- hydroxypropyl) benzamid e hydrochloride	**585.3
3342		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-[[2- furylmethyl) (methyl) am ino]methyl)-5- methylbenzamide hydrochloride	**576.4
3343		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-[[2- methoxyethyl) (methyl) a mino]methyl)-5- methylbenzamide hydrochloride	**554.5
3344		3-[[[2- (diethylamino) ethyl] (m ethyl) amino]methyl]-N- ((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)-5- methylbenzamide hydrochloride	**595.4

3345		N-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-2-methoxyacetamide	**457
3346		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[4-(ethoxymethyl)piperidin-1-yl]pentanamide (2:1)	
3347		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-oxoindane-5-carboxamide	**493.2
3348		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-hydroxyindane-5-carboxamide	**495.2
3349		formic acid compound with N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(4-propoxypiperidin-1-yl)acetamide (2:1)	
3350			**614.3
3351			**628.3

3352		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[isobutyl(methyl)amino]methyl]-5-methylbenzamide hydrochloride	**552.5
3353		formic acid compound with 2-(1-butyl-2-oxopiperidin-4-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide (1:1)	
3354		formic acid compound with 2-(4-butylpiperazin-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide (3:1)	
3355		4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide or ELAN157245	
3357		2-[(2S)-4-butyl-2-methyl-3-oxopiperazin-1-yl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide hydrochloride	
3358		2-[(2R)-4-butyl-2-methyl-3-oxopiperazin-1-yl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide hydrochloride	

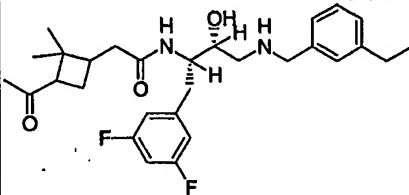
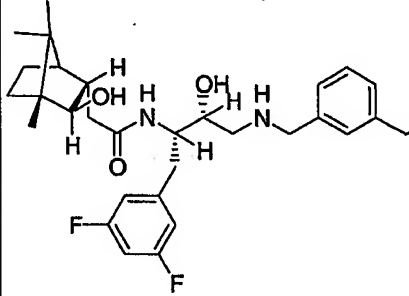
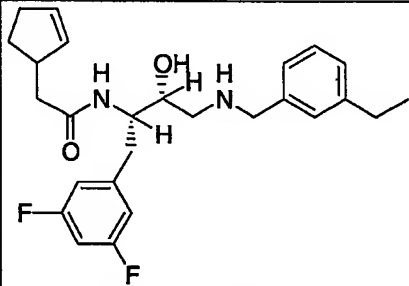
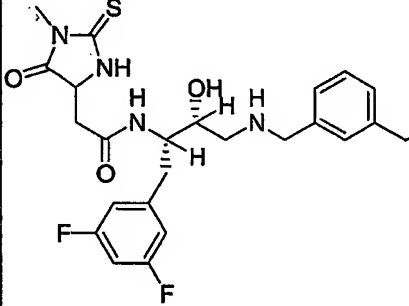
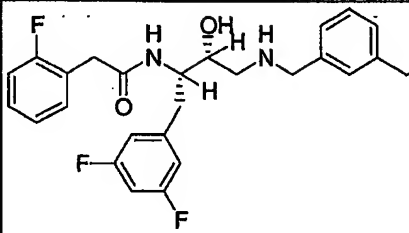
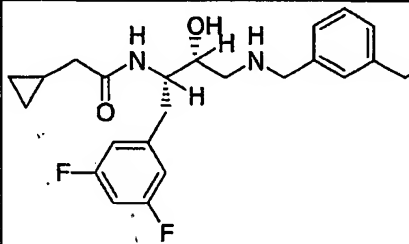
3359		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(2,3-dioxo-4-propylpiperazin-1-yl)acetamide hydrochloride	
3360		4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide hydrochloride	**551
3361		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-methyl-5-([methyl(pentyl)amino]methyl)benzamide hydrochloride	**566.5
3362		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-([(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl)-5-methylbenzamide hydrochloride	**580.4
3363		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([(1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide	
3364		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-([(1-(4-((dimethylamino)methyl)pyridin-2-yl)cyclopropyl]amino)-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	*689

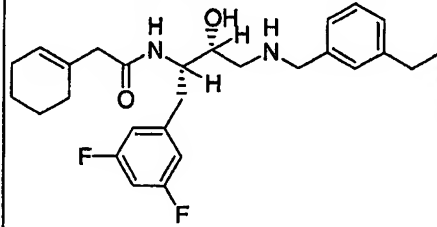
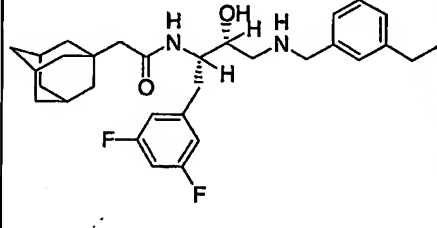
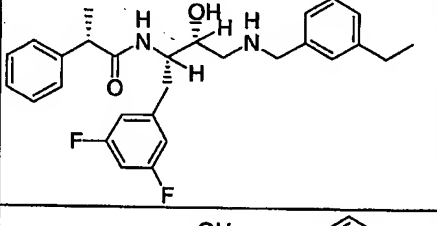
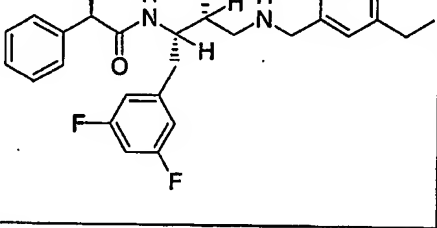
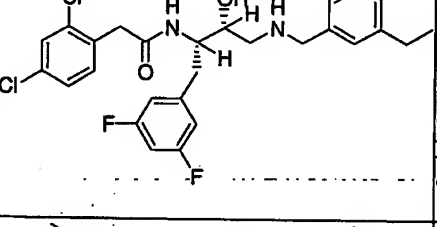
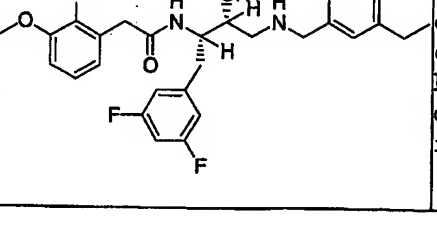
3365		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(dipropylamino)-4-methyl-1,3-thiazole-5-carboxamide	
3367		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-3-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide	
3368		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[(4R)-6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino]-2-hydroxypropyl)-3,5-dimethylbenzamide	**616.2
3370		3-bromo-5-[[butyl(methyl)amino]methyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	
3371		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-1H-indole-6-carboxamide	
3372		ALB 12052 or N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)-3-[[(4-((dimethylamino)methyl)pyridin-2-yl)methyl]amino]-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N ³ ,N ³ -dipropylisophthalamide	*663

3373		3- [(butylamino)methyl]- N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-5- methylbenzamide hydrochloride	**538.5
3374		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-3- [[(2S)-2- (methoxymethyl)pyrroli- din-1-yl]methyl]-5- methylbenzamide hydrochloride	**580.4
3375		formic acid compound with N-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-2-[4- (2- methoxyethyl)piperidin- 1-yl]acetamide (2:1)	
3376		1-butyl-N-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)- 1,2,3,4- tetrahydroisoquinoline -7-carboxamide	**550.4
3377		N¹-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-N¹,5- dimethyl-N³,N³- dipropylisophthalamide	
3378		N¹-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-5-[3- (dimethylamino)prop-1- ynyl]-N³,N³- dipropylisophthalamide	

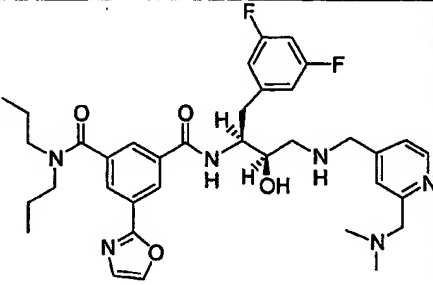
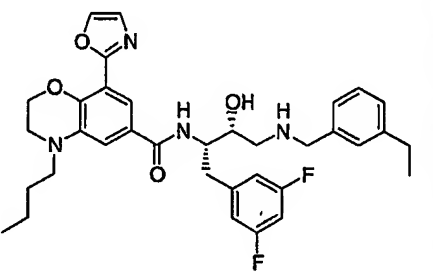
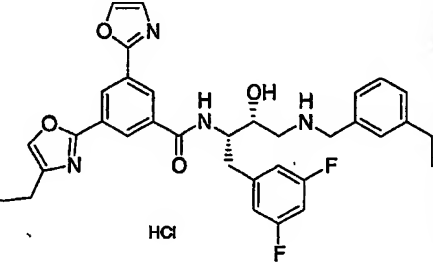
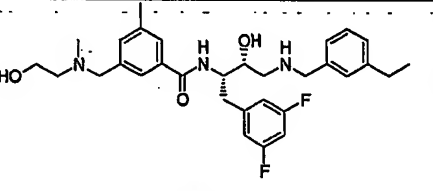
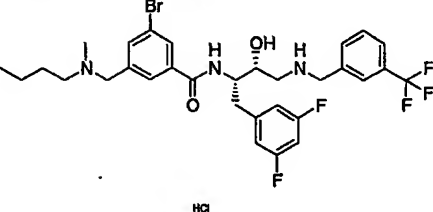
3379		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-phenoxyphenyl)acetamide
3380		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2,5-dimethylphenyl)acetamide
3381		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[2-(trifluoromethoxy)phenyl]acetamide
3382		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-ethoxyphenyl)acetamide
3383		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[2-(trifluoromethyl)phenyl]acetamide
3384		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-methoxyphenyl)acetamide

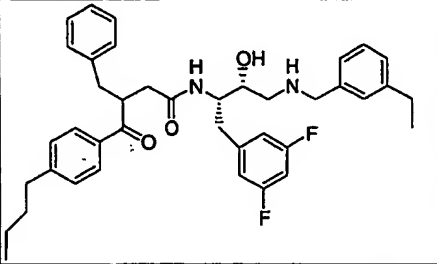
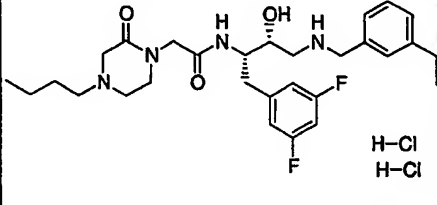
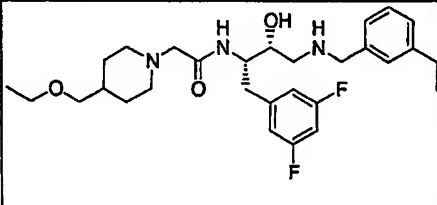
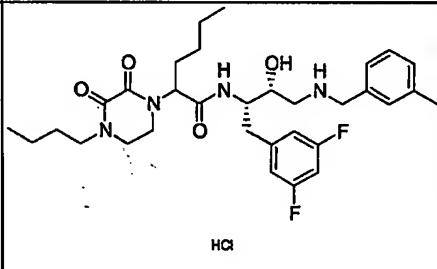
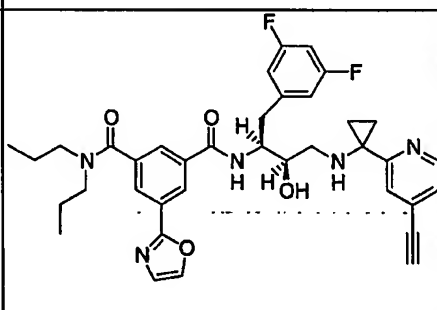
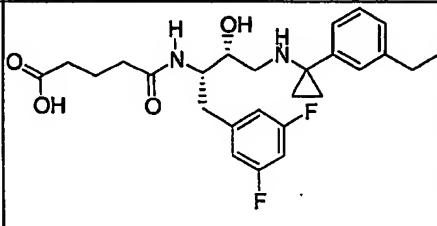
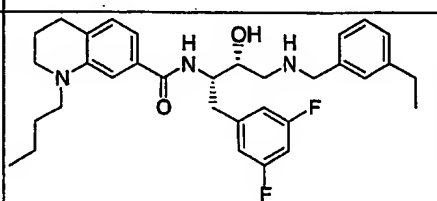
3385		2-[2-(benzyloxy)phenyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]acetamide	
3386		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-phenylbutanamide	
3387		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-mesitylacetamide	
3388		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(2,4-dimethoxyphenyl)acetamide	
3389		2-(2-chlorophenyl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]acetamide	
3390		2-cyclohexyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]acetamide	

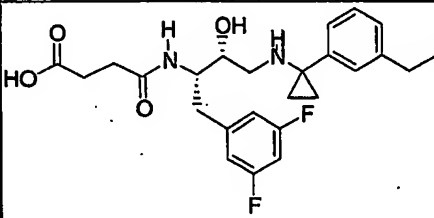
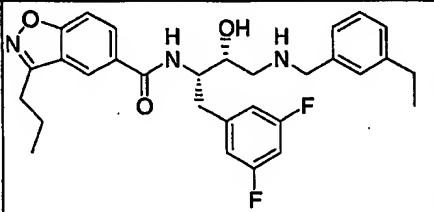
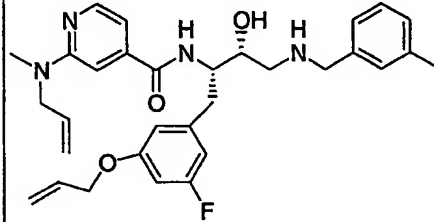
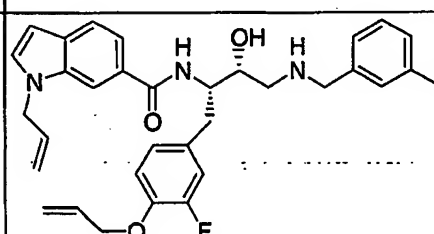
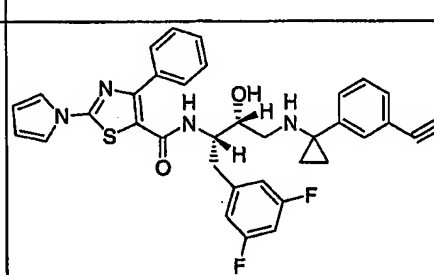
3391		ELAN-157393	
3392		ELAN-157394	
3393		2-cyclopent-2-en-1-yl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	
3394		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1-methyl-5-oxo-2-thioxoimidazolidin-4-yl)acetamide	
3395		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-fluorophenyl)acetamide	
3396		2-cyclopropyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	

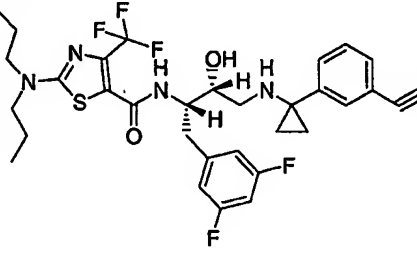
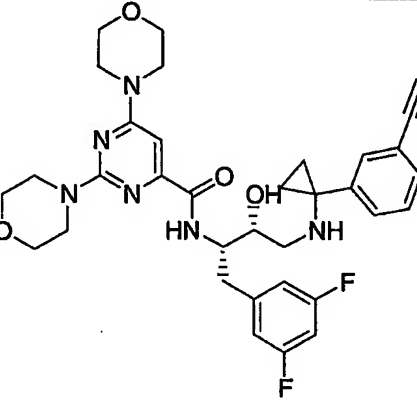
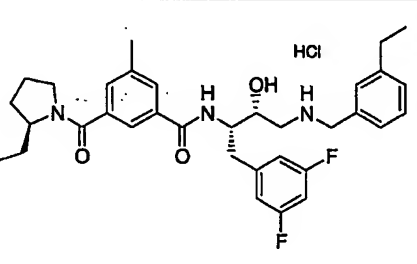
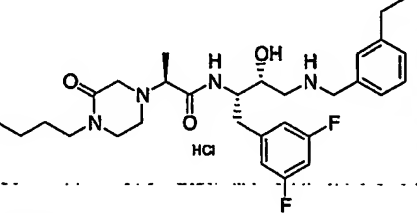
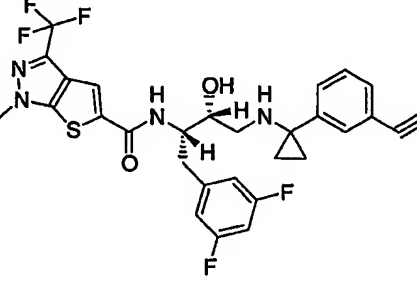
3397		2-cyclohex-1-en-1-yl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	
3398		2-(1-adamantyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	
3399		(2S)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylpropanamide	
3400		(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylpropanamide	
3401		2-(2,4-dichlorophenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	
3402		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2,3-dimethoxyphenyl)acetamide	

3403		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[3-(dimethylamino)propyl]-N³,N³-dipropylisophthalamide	
3406		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(4-ethynylpyridin-2-yl)cyclopropyl]amino]-2-hydroxypropyl)-5-[(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3407		4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide 1-oxide	
3408		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-heptyl-4-hydroxy-L-prolinamide	
3409		2-[butyl(methyl)amino]-6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide	
3410		2-[butyl(methyl)amino]-6-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)isonicotinamide	

3411		ALB-12164 N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-(((2-((dimethylamino)methyl)pyridin-4-yl)methyl)amino)-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N,N-dipropylisophthalamide	*663
3412		4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-(((3-ethylbenzyl)amino)-2-hydroxypropyl)-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide or 4-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-(((3-ethylbenzyl)amino)-2-hydroxypropyl)-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide	**619
3413		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-(((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(4-ethyl-1,3-oxazol-2-yl)-5-(1,3-oxazol-2-yl)benzamide hydrochloride	**601
3414			**540.4
3415			**656.2

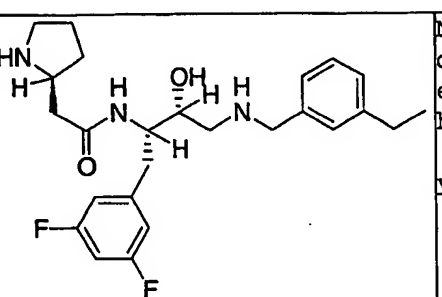
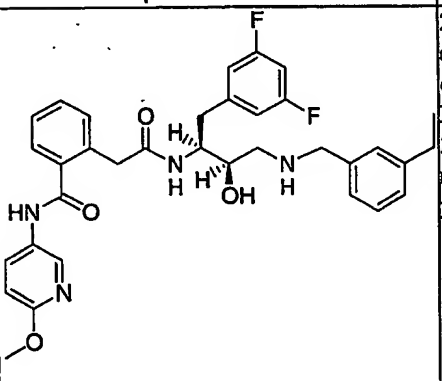
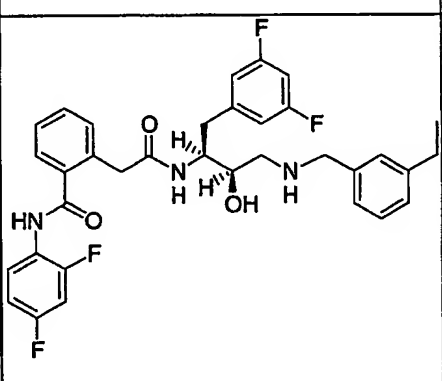
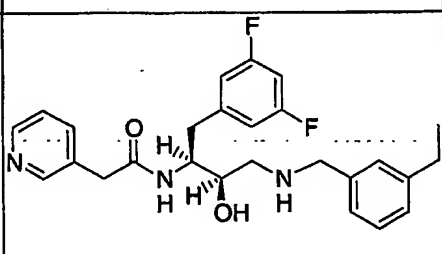
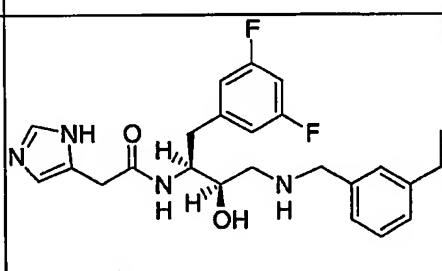
3416		3-benzyl-4-(4-butylphenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxobutanamide	**641.6
3417		2-(4-butyl-2-oxopiperazin-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide dihydrochloride	
3418		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[4-(ethoxymethyl)piperidin-1-yl]acetamide	
3419		2-(4-butyl-2,3-dioxopiperazin-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)hexanamide hydrochloride	
3421		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(4-ethynylpyridin-2-yl)cyclopropyl]amino]-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide	
3422		5-(((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)amino)-5-oxopentanoic acid	**475.2
3423		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,2,3,4-tetrahydroquinoline-6-carboxamide	

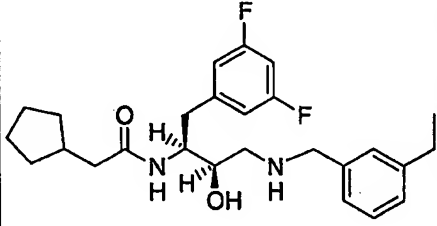
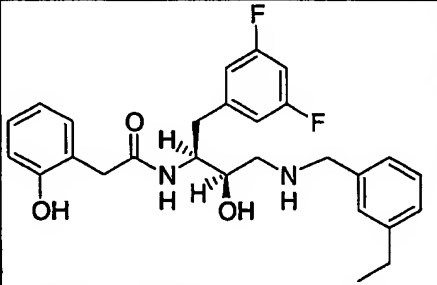
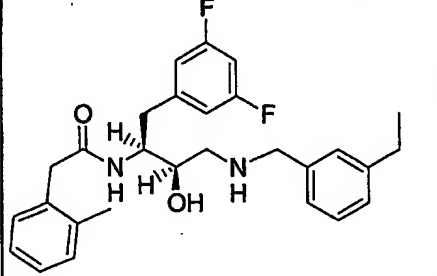
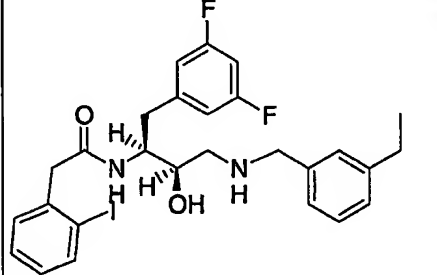
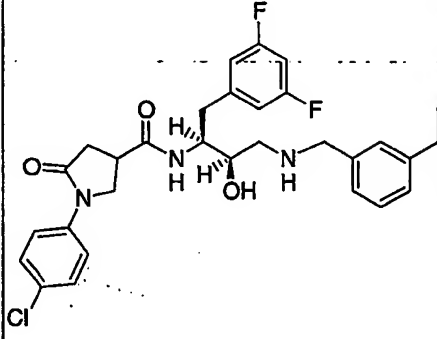
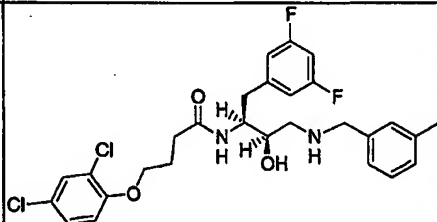
		tetrahydroquinoline-7-carboxamide or 1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,2,3,4-tetrahydroquinoline-7-carboxamide	
3424		4-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]amino]-4-oxobutanoic acid	**461.2
3425		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-propyl-1,2-benzisoxazole-5-carboxamide	
3426		2-[allyl(methyl)amino]-N-((1S,2R)-1-[3-(allyloxy)-5-fluorobenzyl]-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]isonicotinamide	**547.5
3427		1-allyl-N-((1S,2R)-1-[4-(allyloxy)-3-fluorobenzyl]-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-6-carboxamide	**556.4
3428		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-4-phenyl-2-(1H-pyrrol-1-yl)-1,3-thiazole-5-carboxamide	

3429		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-(dipropylamino)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide	
3432		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2,6-dimorpholin-4-ylpyrimidine-4-carboxamide	
3433		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[2-(2-ethylpyrrolidin-1-yl)carbonyl]-5-methylbenzamide hydrochloride	
3434		(2S)-2-(4-butyl-3-oxopiperazin-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)propanamide hydrochloride	
3451		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-1-methyl-3-(trifluoromethyl)-1H-thieno[2,3-c]pyrazole-5-carboxamide	

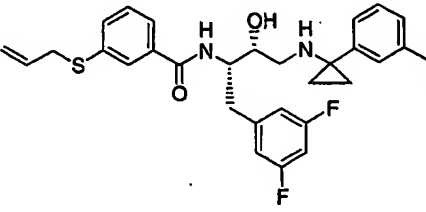
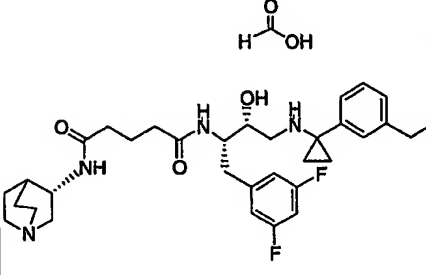
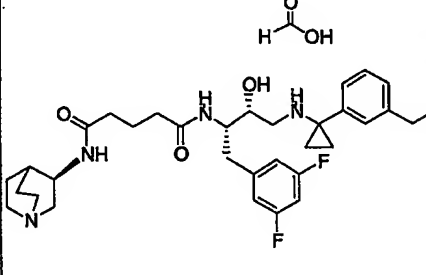
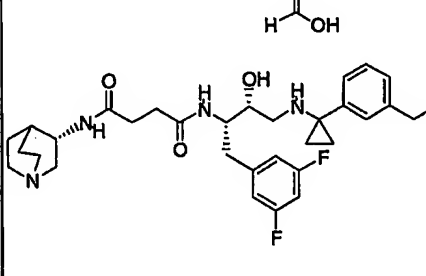
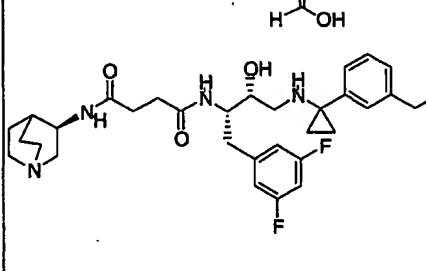
3452		2-[allyl(methyl)amino]-N-[(1S,2R)-1-[4-(allyloxy)-3-fluorobenzyl]-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]isonicotinamide	**547.4
3453		3-butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1,2-benzisoxazole-5-carboxamide	**536
3454		5-(3-aminopropyl)-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N³,N³-dipropylisophthalamide	
3455		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-[3-(methylamino)propyl]-N³,N³-dipropylisophthalamide or ELAN157961	
3456		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-[3-(methylamino)prop-1-ynyl]-N³,N³-dipropylisophthalamide	
3457		5-(3-aminoprop-1-ynyl)-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N³,N³-dipropylisophthalamide or ELAN157963	

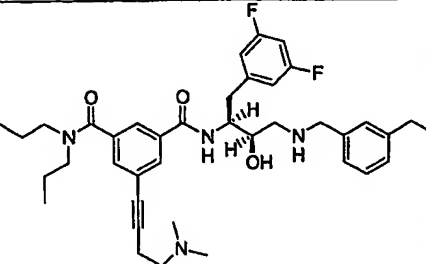
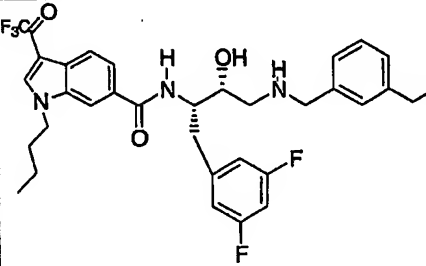
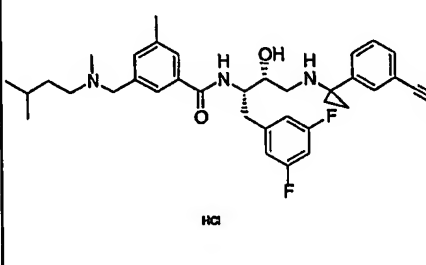
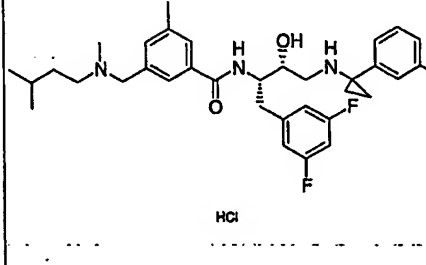
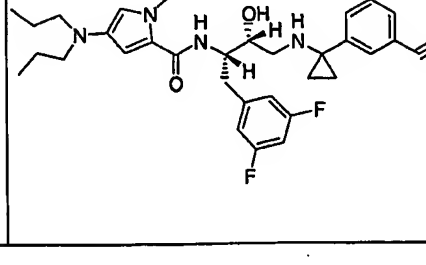
3458		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-5-pyrrolidin-1-ylpyrazine-2-carboxamide	
3459		4-butoxy-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)quinoline-2-carboxamide	
3461		2-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-[methyl(propyl)amino]isonicotinamide	
3462		3-acetyl-1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indole-6-carboxamide	
3463		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-indol-6-ylmethyl)amino]propyl)-5-methyl-N³,N³-dipropylisophthalamide	**591.5
3464		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-isobutyl-1,2-benzisoxazole-5-carboxamide	**536

3465		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((2S)-pyrrolidin-2-yl)acetamide	
3466		2-[2-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)-2-oxoethyl]-N-(6-methoxypyridin-3-yl)benzamide	
3467		2-[2-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)-2-oxoethyl]-N-(2,4-difluorophenyl)benzamide	
3468		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-pyridin-3-ylacetamide	
3469		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(1H-imidazol-5-yl)acetamide	

3470		2-cyclopentyl-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid e	
3471		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-2-(2- hydroxyphenyl)acetamid e	
3472		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-2-(2- methylphenyl)acetamide	
3473		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-2-(2- iodophenyl)acetamide	
3474		1-(4-chlorophenyl)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5- oxopyrrolidine-3- carboxamide	
3475		4-(2,4- dichlorophenoxy)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}butanami de	

3476		4,5-dibromo-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thiophene-2-carboxamide	
3477		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	
3478		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2,6-bis(dimethylamino)pyrimidine-4-carboxamide	
3479		4-butyl-8-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide	**577
3480		3-(allylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)benzamide	**569.8

3481		3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)benzamide	**537.8
3484		formic acid compound with N¹-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)pentanediamide (1:1)	**583.3
3485		formic acid compound with N¹-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-N⁵-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)pentanediamide (1:1)	**583.3
3486		formic acid compound with N¹-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)succinamide (1:1)	**569.3
3487		formic acid compound with N¹-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)succinamide (1:1)	**569.3

3490		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[4-(dimethylamino)but-1-ynyl]-N³,N³-dipropylisophthalamide or ELAN158095	
3491		1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(trifluoroacetyl)-1H-indole-6-carboxamide	
3492		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[[isopentyl(methyl)amino]methyl]-5-methylbenzamide hydrochloride	**588.3
3493		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[[isopentyl(methyl)amino]methyl]-5-methylbenzamide hydrochloride	**592.3
3494		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-4-(dipropylamino)-1-methyl-1H-pyrrole-2-carboxamide	

3495		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([[(4R)-6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino)-2-hydroxypropyl)-4-(2-methoxyethyl)benzamide	
3496		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[4-(dimethylamino)butyl]-N³,N³-dipropylisophthalamide or ELAN158113	
3497		ELAN-158116	
3500		ELAN-158128 2,6-dichloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)pyrimidine-4-carboxamide	
3503		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-morpholin-4-yl-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide	

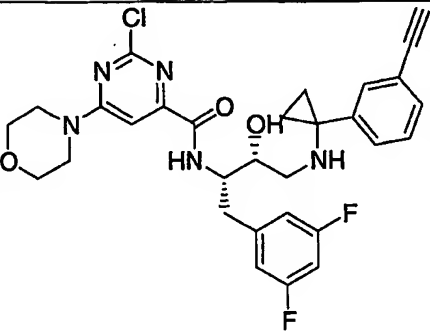
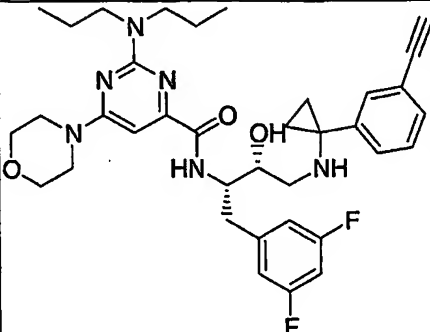
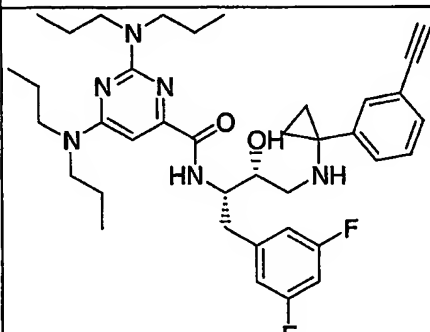
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3507		**648
3508		**553.8
3520		
3521		
3522		

3523		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2'-ethoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3524		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-3'-(trifluoromethoxy)-1,1'-biphenyl-3-carboxamide
3525		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4'-propoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3526		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4'-(dimethylamino)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3527		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2'-propoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3528		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3'-propoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide

3529		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl)-3-[(3-ethoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamido]benzyl)-2-hydroxypropyl)-4'-ethoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3530		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl)-4'-ethoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3531		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl)-4'-isopropoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3532		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl)-4'-(hydroxymethyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3533		4'-butoxy-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3534		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-4'-methoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide

3535		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carboxamide
3536		4'-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3537		3'-butoxy-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3538		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3'-(isopropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3539		3'-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3540		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2'-methyl-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide

3541		2'-acetyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3542		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4'-hydroxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3543		4'-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide
3544		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(1H-pyrrol-2-yl)-5-(1,3-thiazol-2-yl)benzamide
3545		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((E)-2-(4-fluorophenyl)ethenyl)-5-(1,3-thiazol-2-yl)benzamide
3546		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((1-(3-ethynylphenyl)cyclopropyl)amino)-2-hydroxypropyl)pyrimidine-4-carboxamide

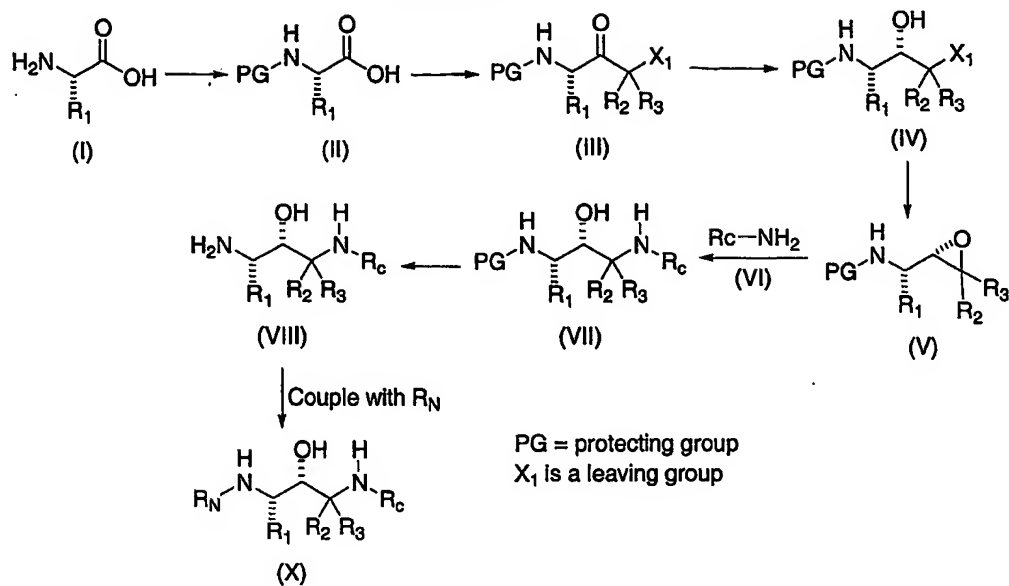
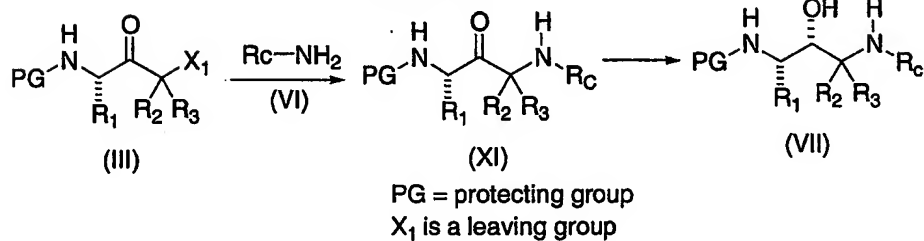
3549		2-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-6-morpholin-4-ylpyrimidine-4-carboxamide
3550		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-(dipropylamino)-6-morpholin-4-ylpyrimidine-4-carboxamide
3551		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2,6-bis(dipropylamino)pyrimidine-4-carboxamide

* means M/Z (EI)

** means M+H (CI)

*** means OAMS

**** means MS Data

CHART A**CHART B**

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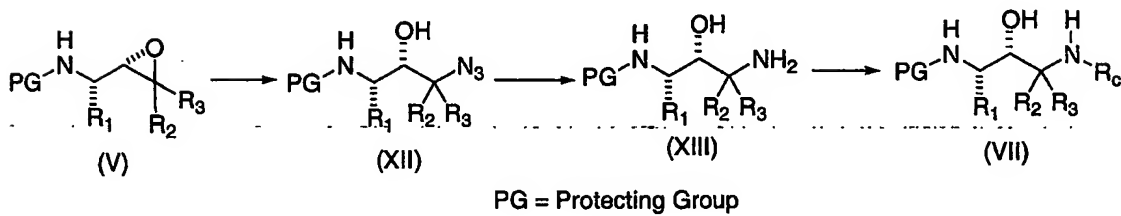
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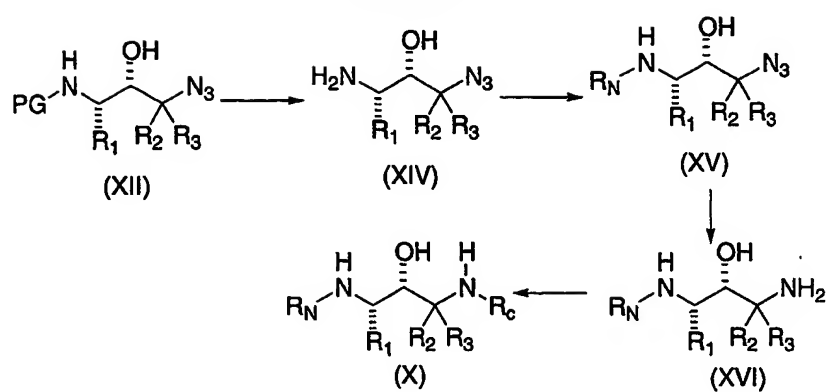
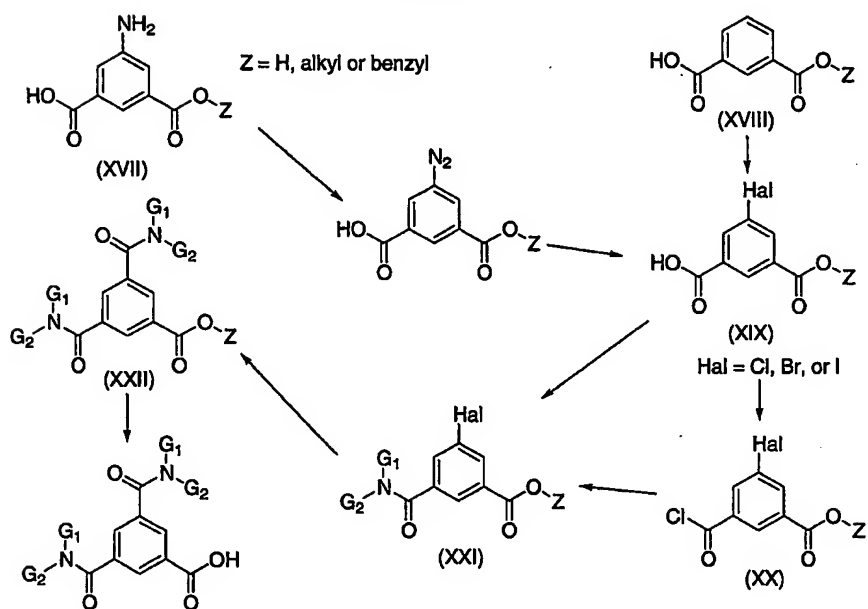
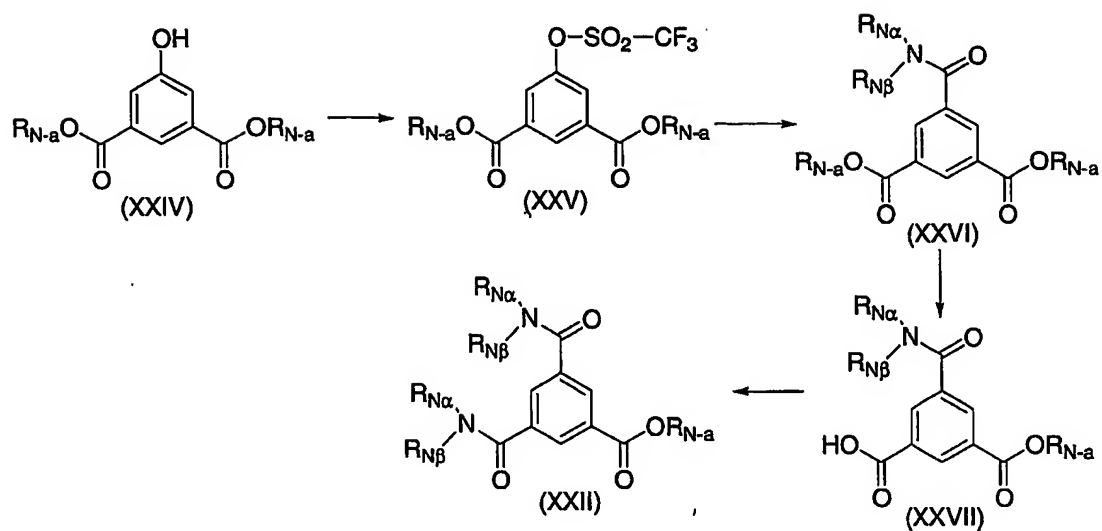
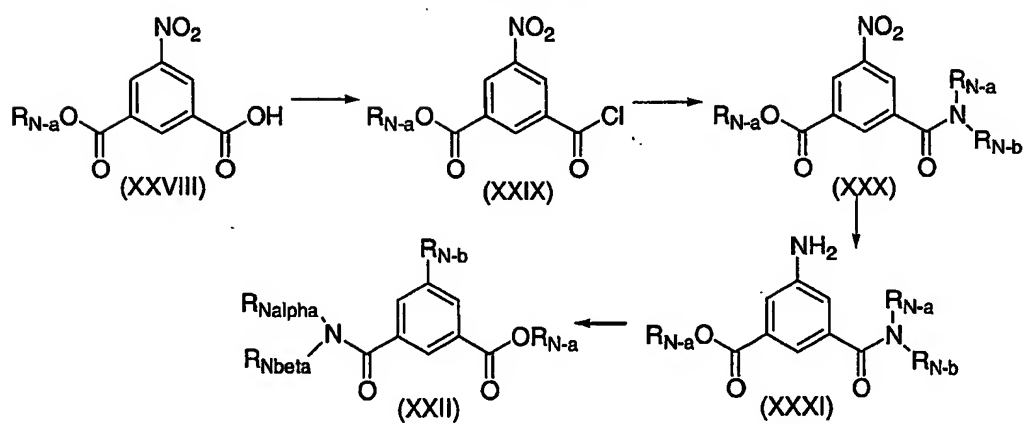
CHART D**CHART E**

CHART F**CHART G**

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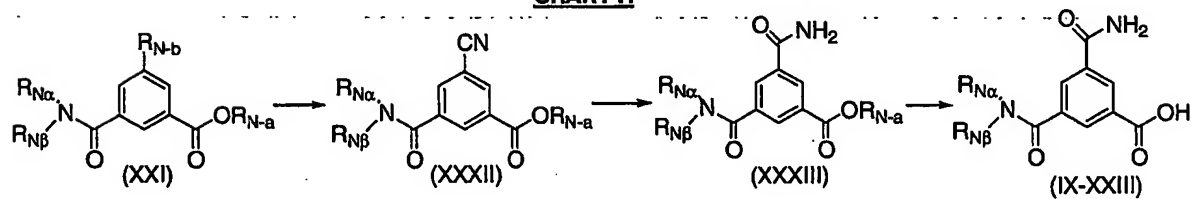
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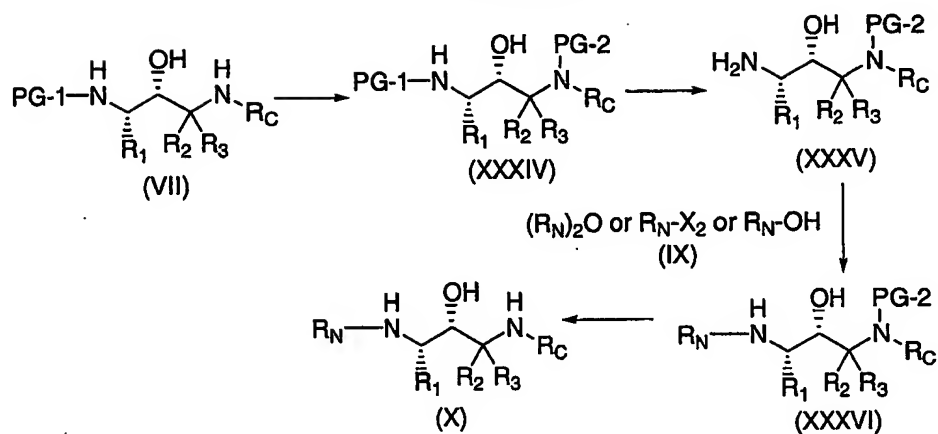
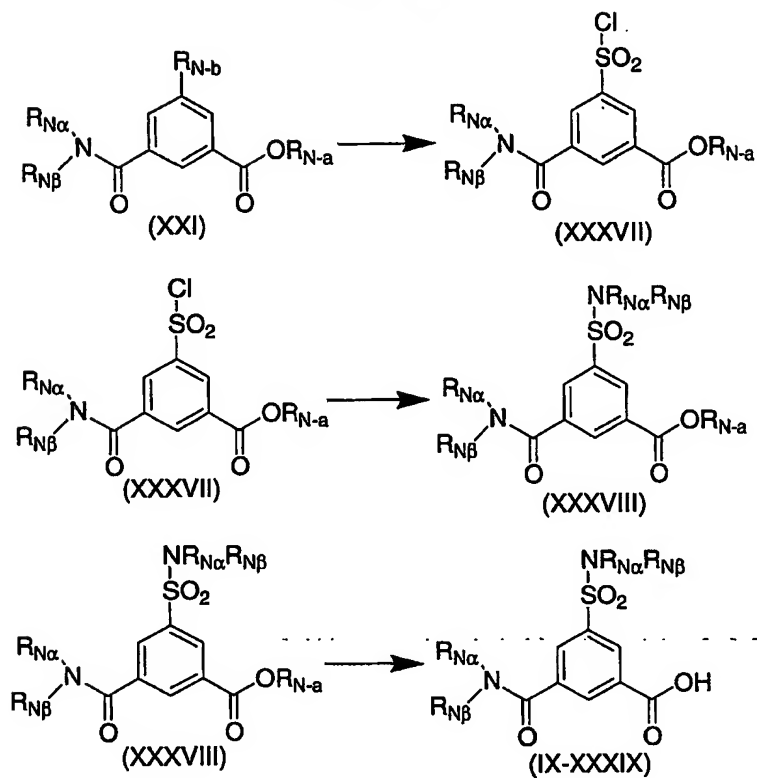
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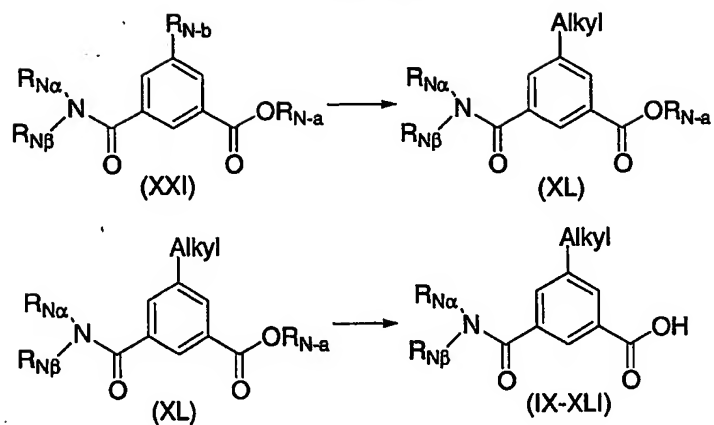
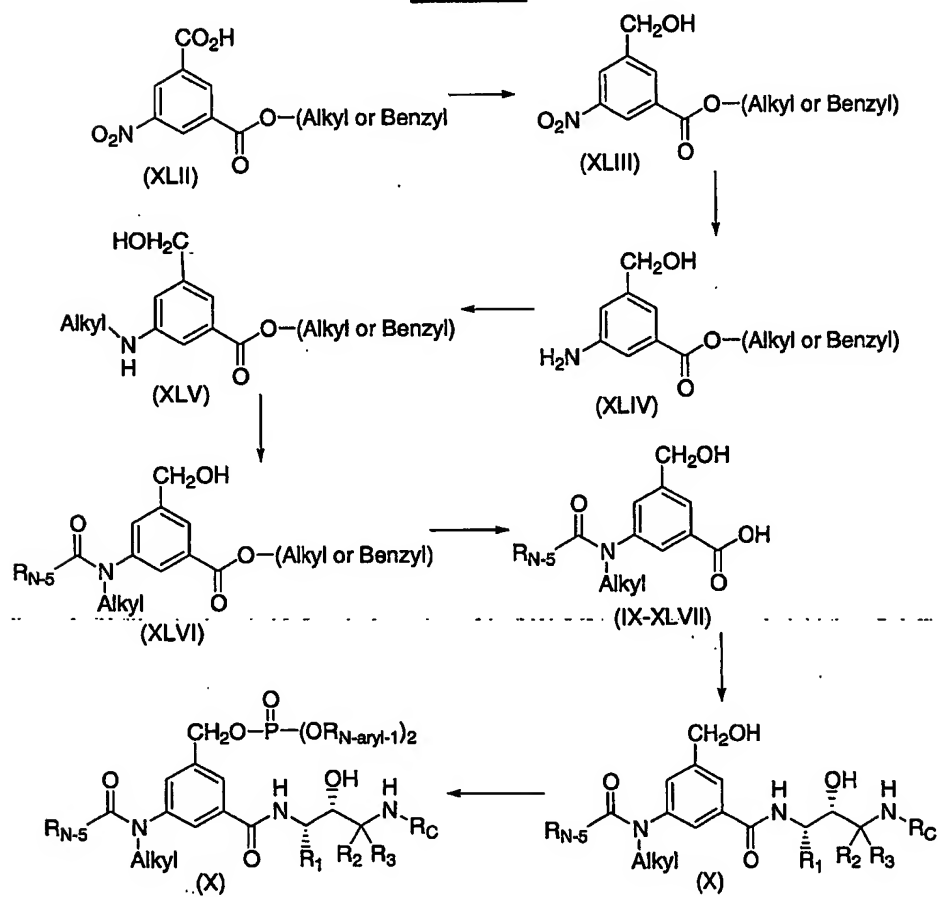
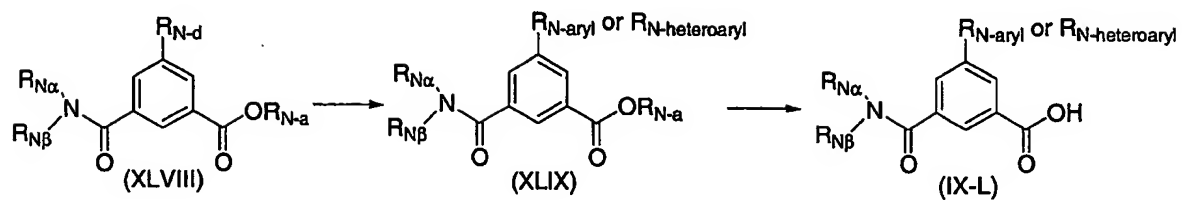
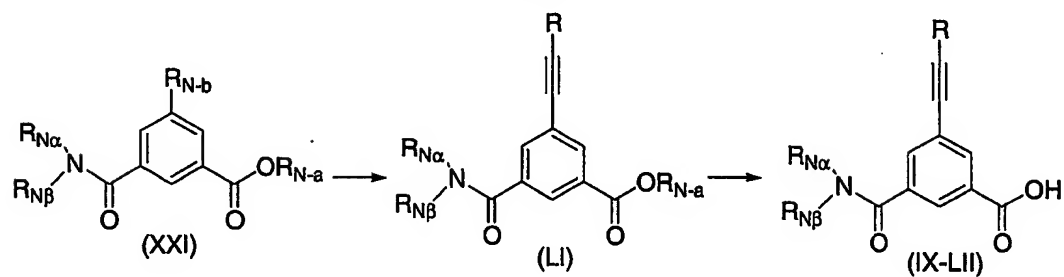
CHART K**CHART L**

CHART M**CHART N**

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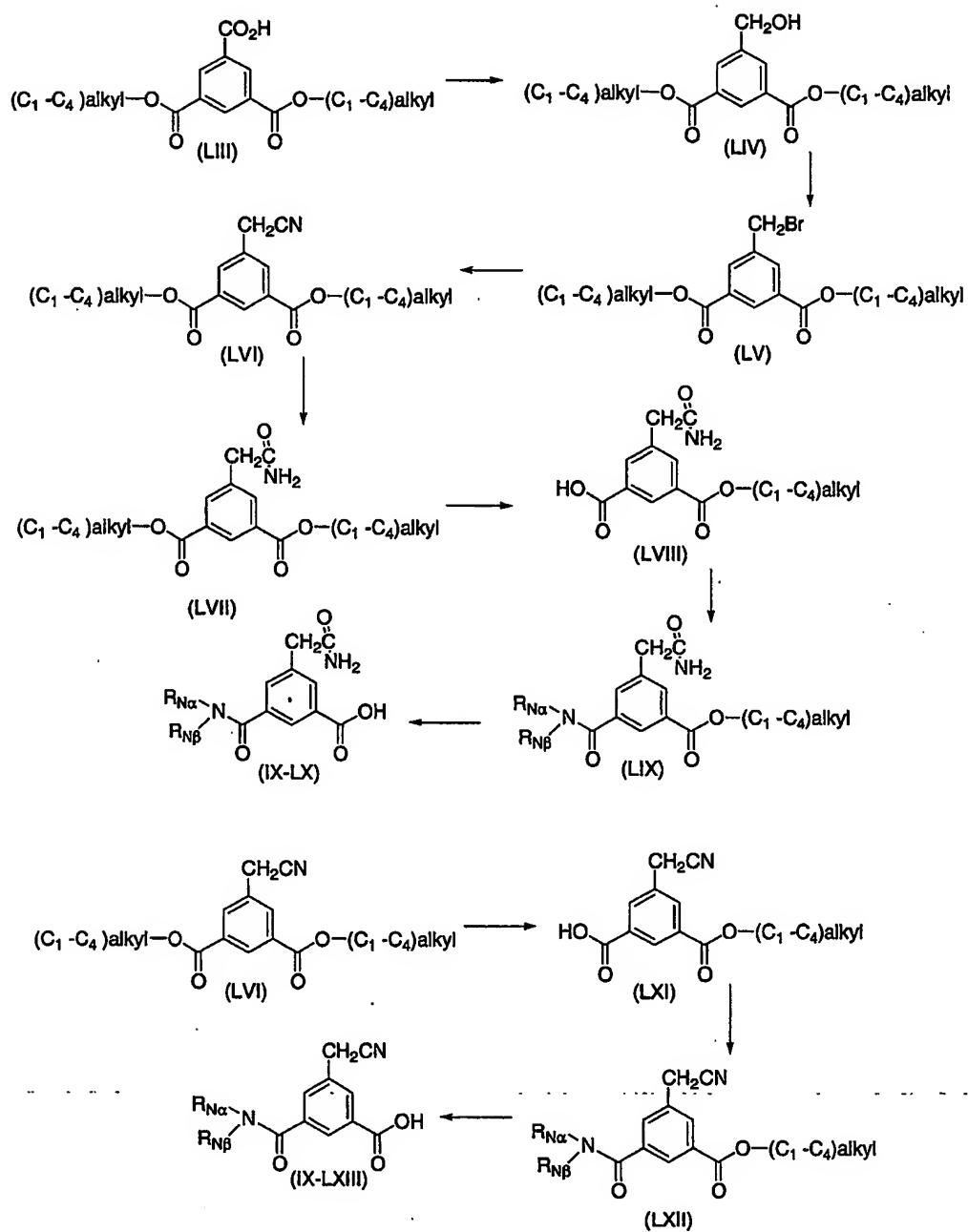
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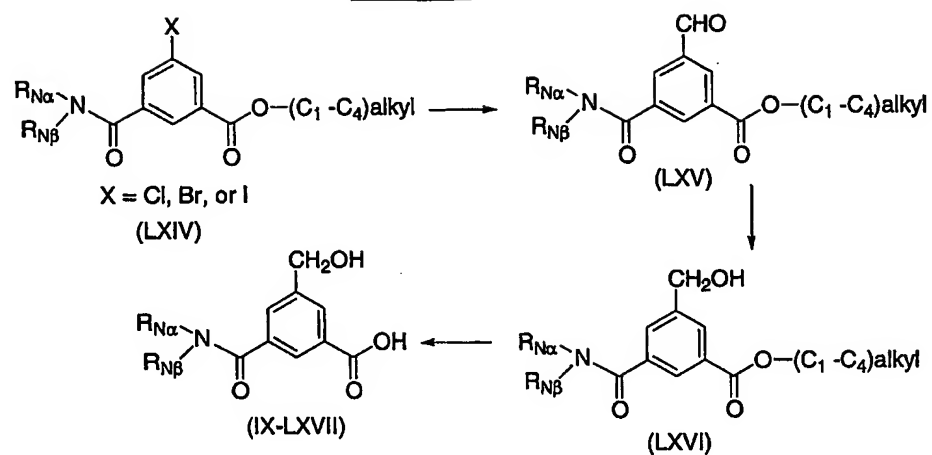
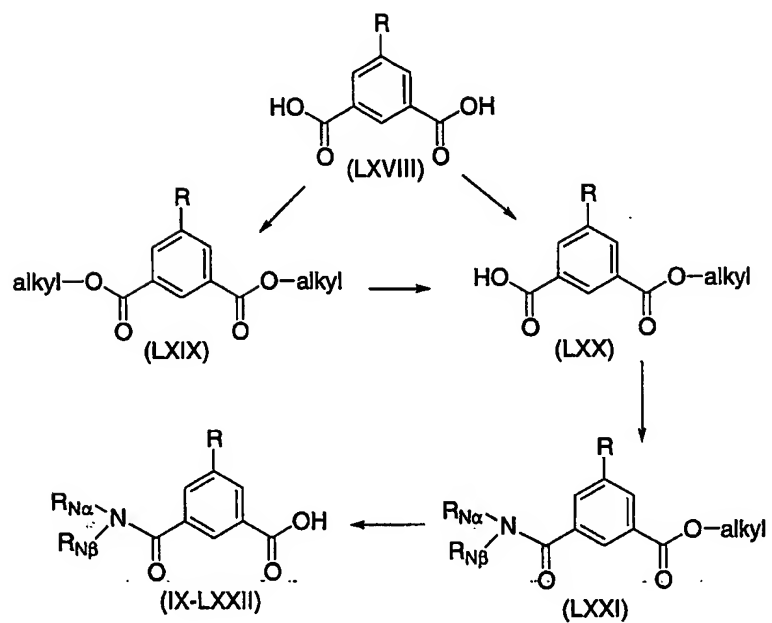
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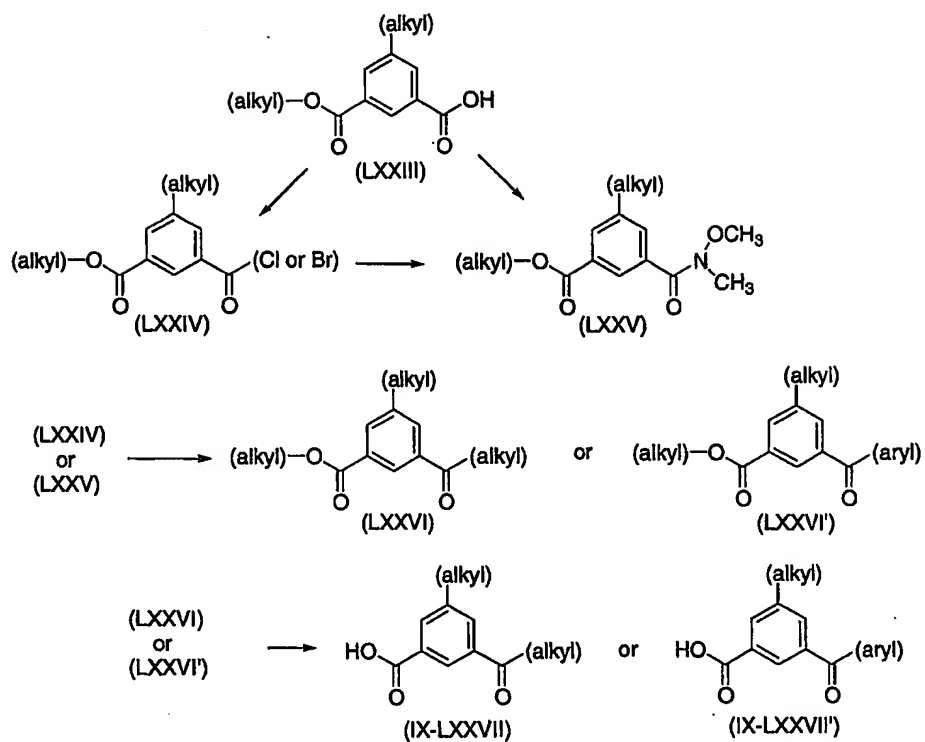
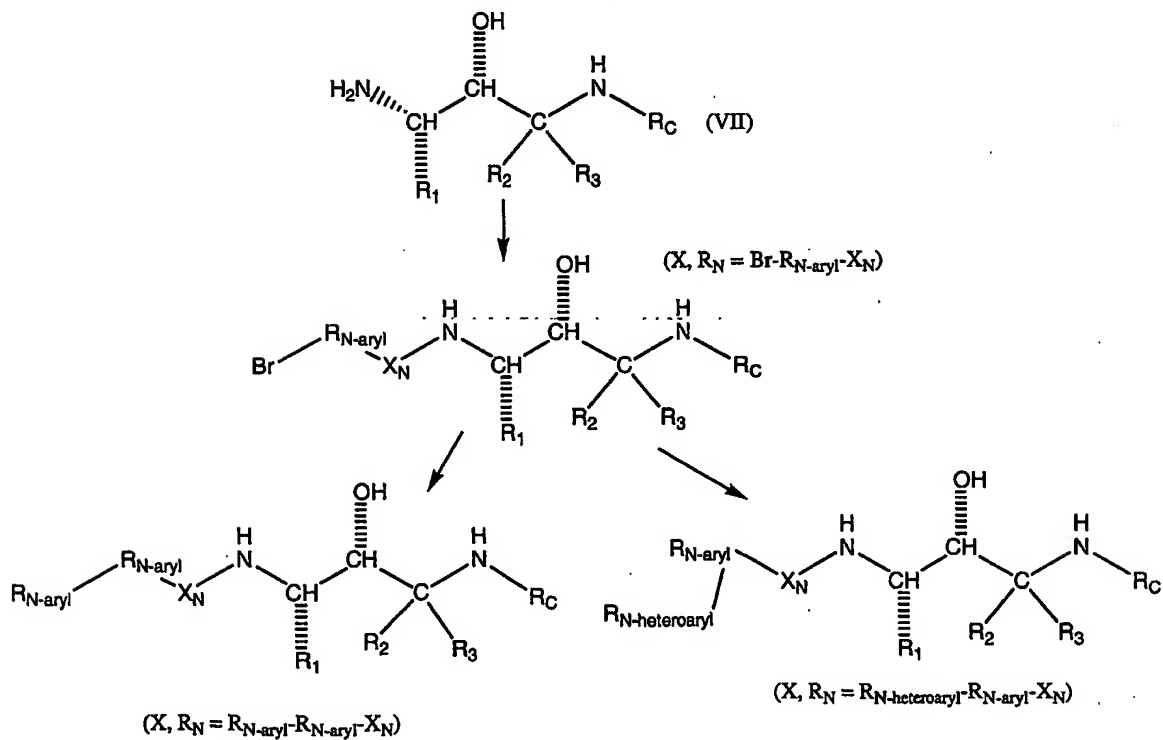
CHART R**CHART S**

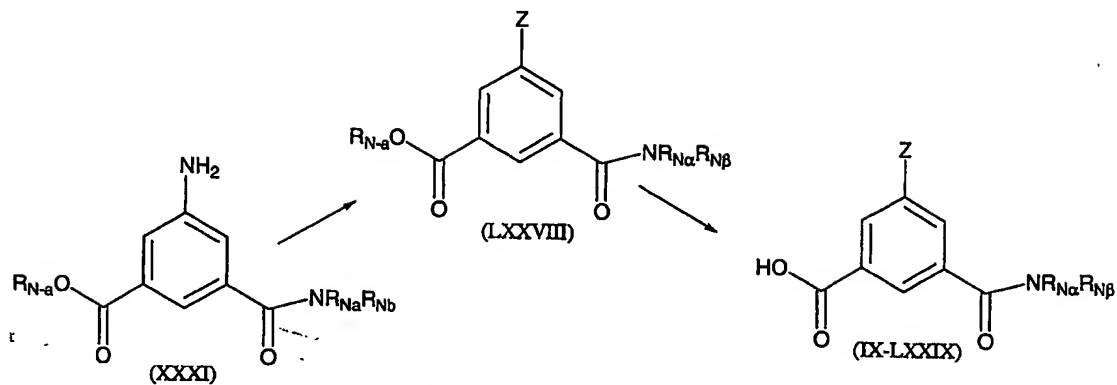
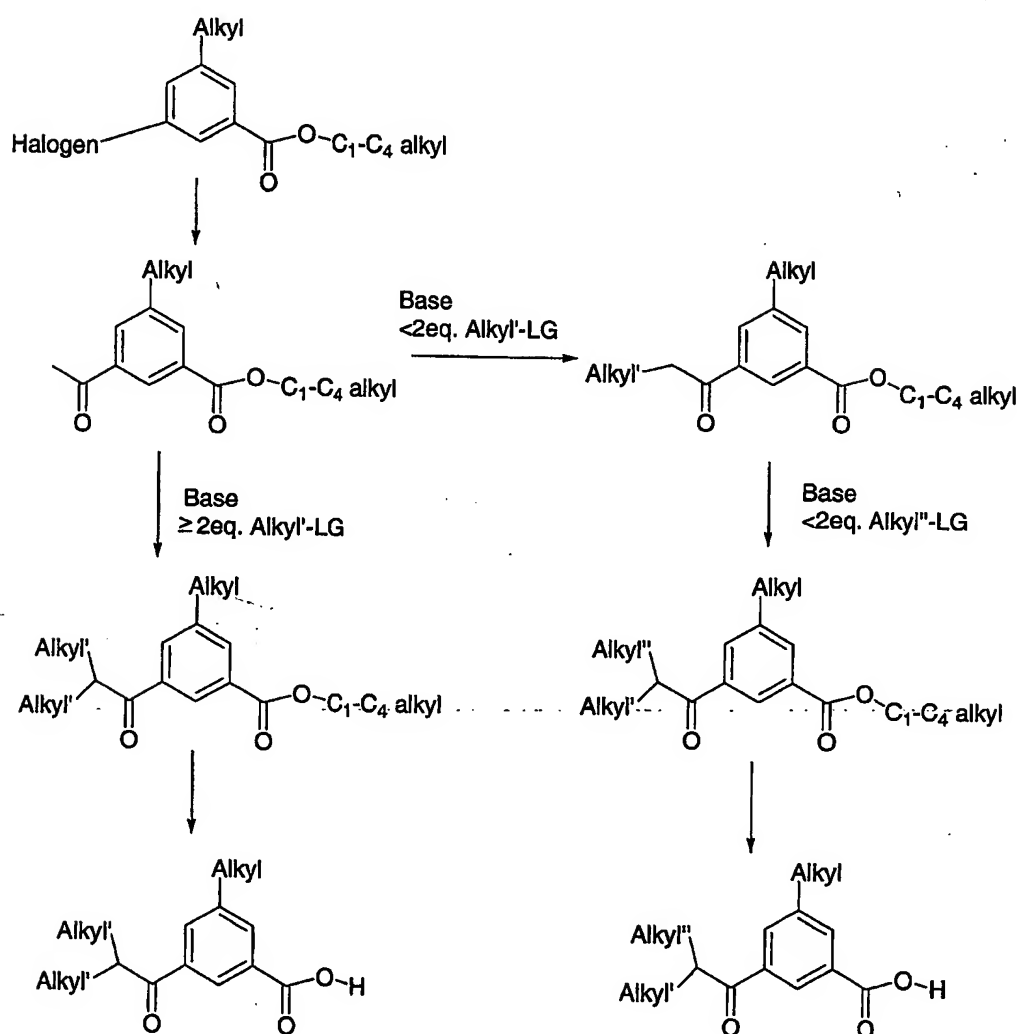
CHART T**CHART U**

CHART U details a method for the preparation of ketones used in the invention. The preferred halogen is bromine or

iodine. A commercially available halogenated benzoate is coupled with (α -ethoxyvinyl)-tributyl in the presence of a catalyst, for example a palladium catalyst like dichlorobis (triphenylphosphine)palladium, yielding a methylketone-

5 substituted benzoate ester after hydrolytic workup. In a preferred embodiment of the invention, this reaction is conducted in an anhydrous organic solvent. In a further more preferred embodiment of the invention, this reaction is conducted in anhydrous toluene. (Kosugi and Migita, *Bull. Chem.*

10 *Soc., Jpn.*, **1987**, *60*, 767-768). Base-catalyzed nucleophilic addition to a stoichiometric excess of alkyl'-LG (or alkyl"-LG) yields a symmetric dialkylated product that, depending on the strength of the base, may be directly converted to the equivalent benzoate. Alternatively, the methylketone-

15 substituted benzoate ester may be reacted with a lower excess of alkyl'-LG, yielding a mono-substituted derivative. Said derivative may be further alkylated by base-catalyzed reaction with alkyl"-LG. It is understood that LG is Leaving Group as defined above. It is understood by one skilled in the art how

20 to perform alkylations. In a preferred embodiment of the invention, said alkylations are catalyzed by sodium hydroxide or potassium hydroxide. In an additional preferred embodiment of the invention, the alkylations are conducted in a dipolar aprotic solvent, e.g. dimethylsulfoxide.

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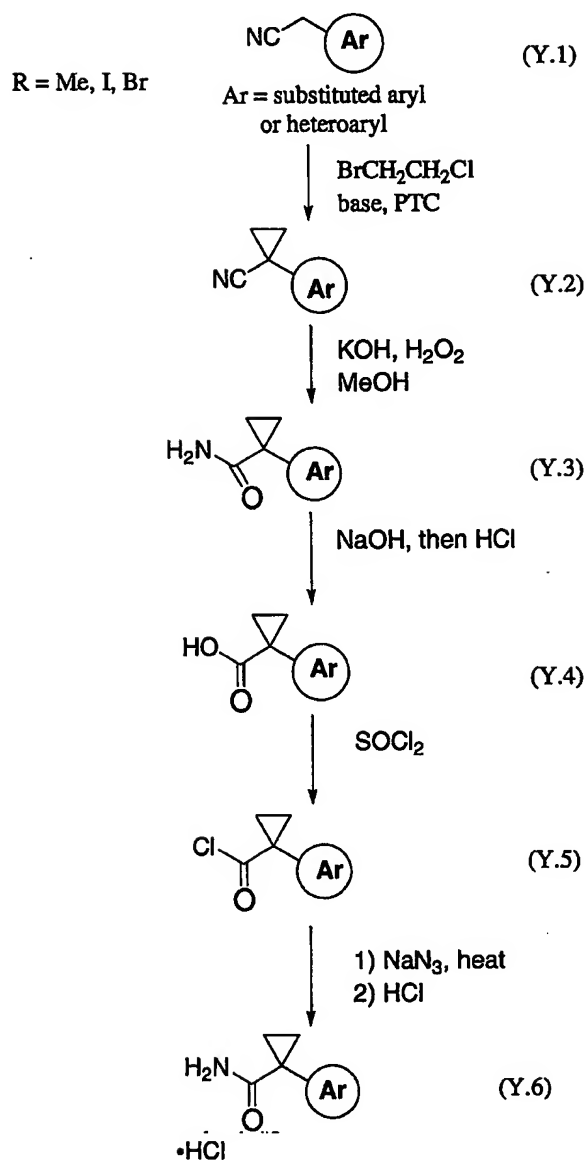
CHART V

CHART V. Synthesis of 3-substituted cyclopropylbenzylamines and related heteroaryl amines (Y.6 in Chart V). A commercially available 3-substituted benzylonitrile is reacted with 1-bromo-2-chloroethane in the presence of an aqueous base and a phase transfer catalyst to yield the a cyclopropanated benzylnitrile (Y.2). The cyanide (Y.2) is converted to amide (Y.3), which is treated with aqueous base, yielding acid (Y.4) after acidic workup. Acid (Y.4) is converted to acyl chloride (Y.5), which is reacted

with azide, yielding an intermediate which undergoes rearrangement and decomposition to give product (Y.6). (Y.6) is then reacted according to Chart JJ to yield inhibitor (X). Representative procedures are provided in Example 2353.

5

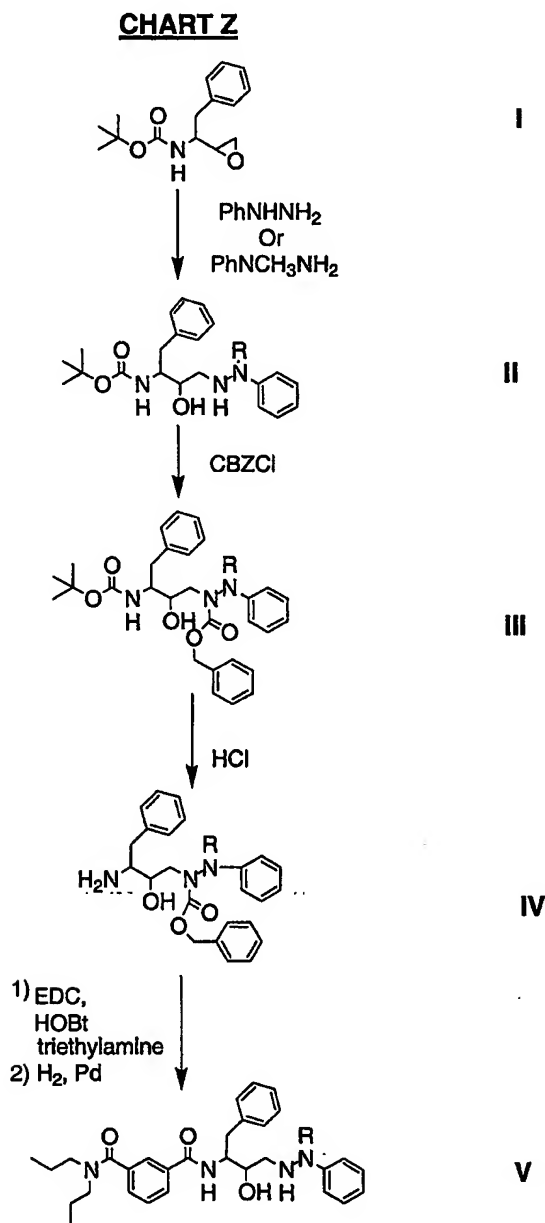
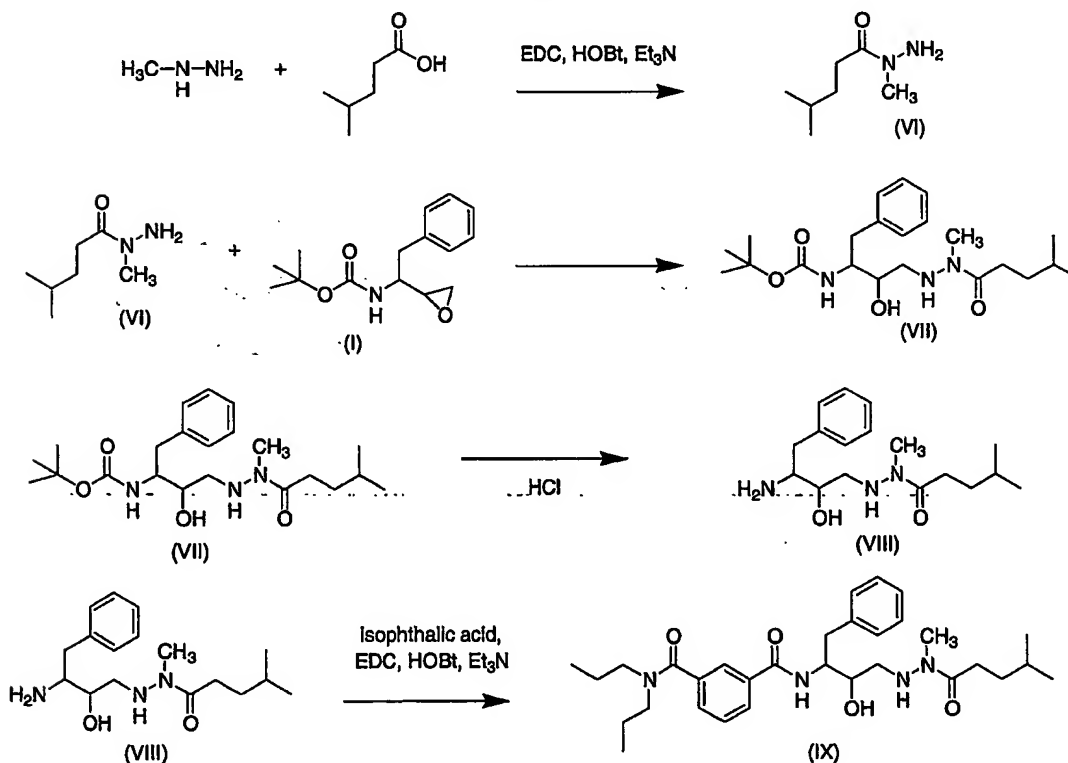


Chart Z. Reaction of epoxide I with an aromatic hydrazine in isopropanol produces the selective alkylation of the unsubstituted hydrazine nitrogen, yielding hydrazine II (M.

Nakakata, *Tetrahedron Letters* **1993**, 6095-6098). Acylation of one of the hydrazine nitrogens with an acylating agent, e.g. benzyloxycarbonyl, yields **III** and reduces the reactivity of this moiety to further acylation irrespective of which

5 hydrazine nitrogen is the first to undergo acylation (B. Gisin, *Helv. Chim. Acta* **1970**, vol 53, 1030-1043. S. Shinagawa, *Chem. Pharm. Bull.* **1981**, vol 29, 3630-3638). Removal of the tert-butoxycarbonyl protecting group of **III** yields free amine **IV**, which is coupled to isophthalic acid (**XIV**) using

10 carbodiimide or other known coupling agents. Deacylation of the hydrazine nitrogen yields compound **V**.

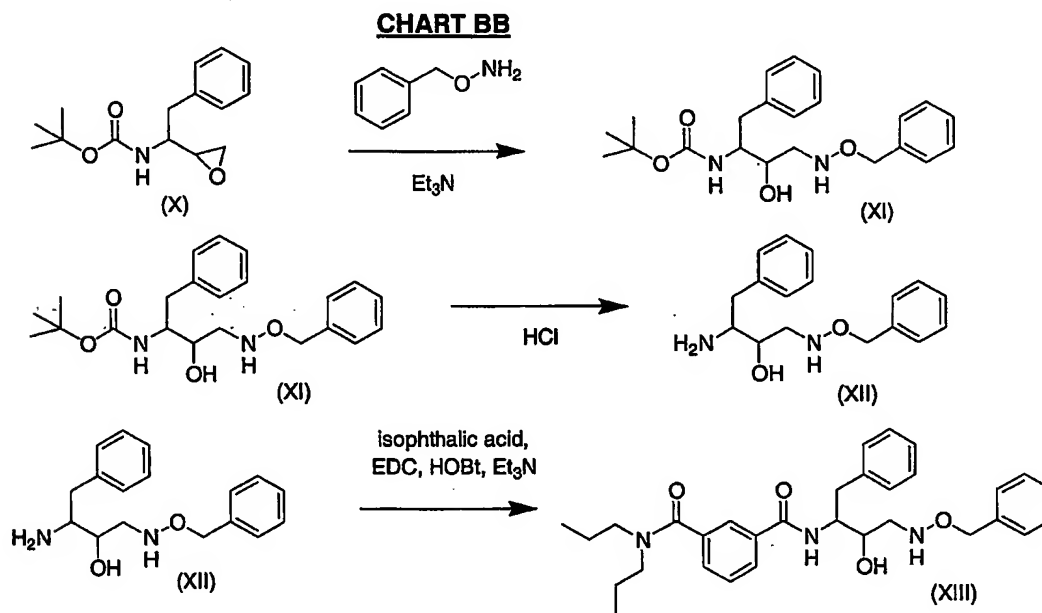
CHART AA

15

CHART AA procedure:

Selective acylation of methylhydrazine on the substituted nitrogen (D. Butler, *J. Medicinal Chemistry* **1971**, vol. 14, 1052-1054) yields acylhydrazine **VI**, which is reacted with

epoxide **I** in isopropanol to form adduct **VII** (S. Wang, *J. Medicinal Chemistry* **1997**, vol 40, 937-941. G. Bold, *J. Medicinal Chemistry* **1998**, vol 41, 3387-3401). Removal of the *tert*-butoxycarbonyl protecting group, followed by coupling to
 5 isophthalic acid (**XIV**) yields final product **IX**.



10 Chart BB procedure:

Epoxide **X** is reacted with *O*-benzylhydroxylamine to yield adduct **XI** (S. Rosenberg, *J. Medicinal Chemistry* **1990**, vol 33, 1582-1590). Removal of the *tert*-butoxycarbonyl protecting
 group, followed by acylation with isophthalic acid **XIV** yields

15 target compound **XIII**.

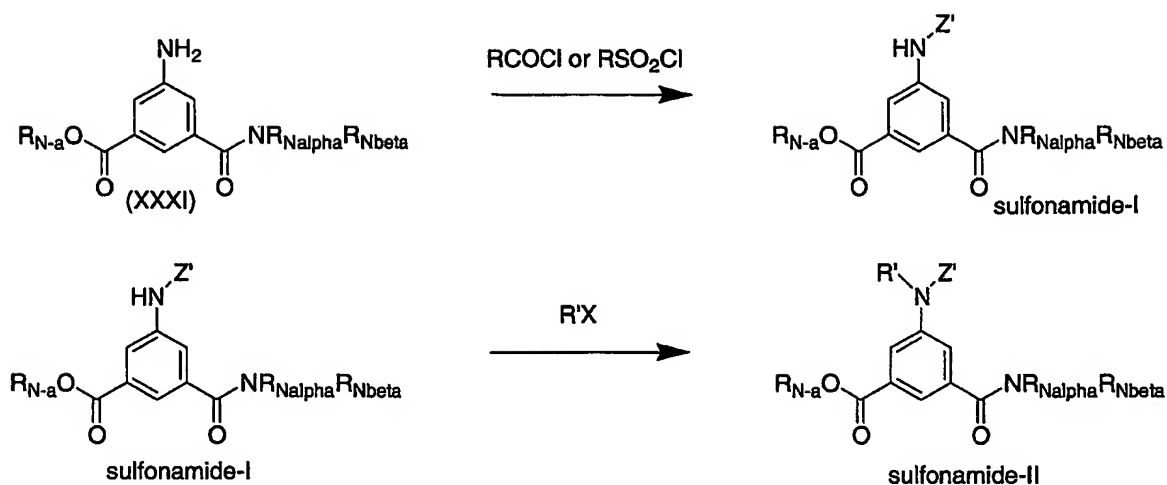
CHART CC

Chart CC. Aniline XXXI is acylated with acyl chlorides or anhydrides or sulfonated with sulfonyl halides or sulfonyl anhydrides to yield sulfonamide-I using methods well known to those skilled in the art. Sulfonamide-I is alkylated with RX, wherein X is a leaving group, for example Cl, Br, tosylate, or mesylate, in the presence of a base, e.g. trialkylamine, sodium hydride, pyridine, or potassium t-butoxide, to yield sulfonamide-II.

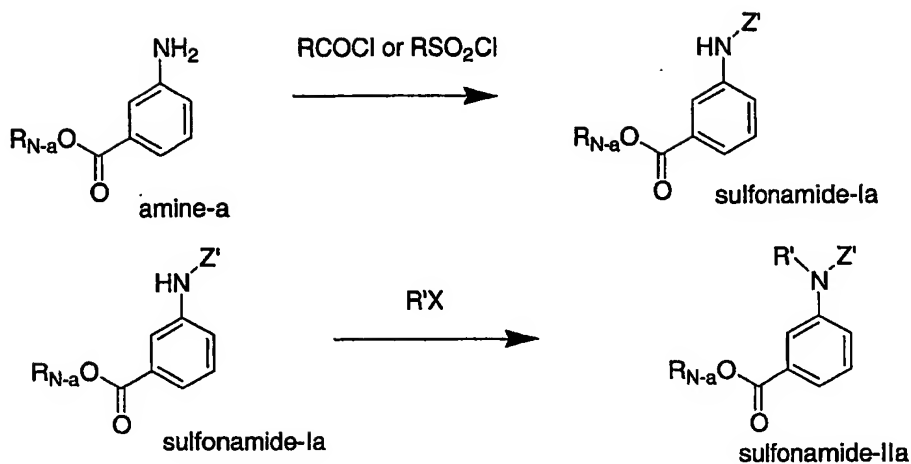
CHART DD

Chart DD. Amine-a is acylated with acyl chlorides or anhydrides or sulfonated with sulfonyl halides or sulfonyl anhydrides to yield sulfonamide-I using methods known to those skilled in the art. Sulfonamide-Ia is alkylated with RX , wherein X is a leaving group, for example Cl, Br, tosylate, or mesylate, in the presence of a base, e.g. trialkylamine, sodium hydride, pyridine, or potassium t-butoxide, to yield sulfonamide-IIa.

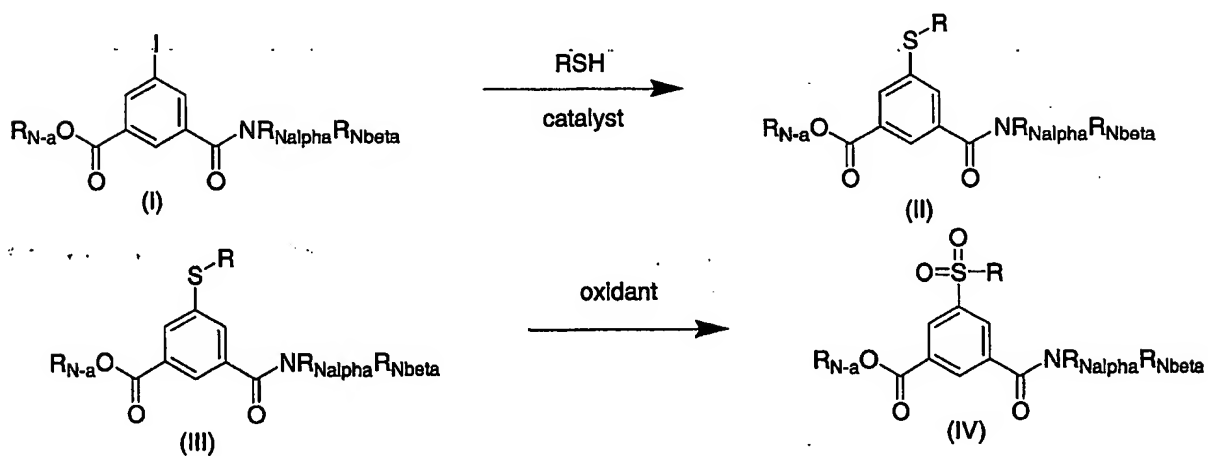
CHART EE

Chart EE. Iodo amide (I) is coupled to a thiol RSH in the presence of a catalyst, for example a palladium (0) catalyst like bis(dibenzylideneacetone) palladium (0), an additive, preferably 1,1'-bis (diphenylphosphino) ferrocene, and a base, e.g. a trialkylamine, in an organic solvent, for example N-methylpyrrolidinone (NMP) or DMF, at a temperature ranging from room temperature to reflux temperature to yield sulfide (II). Sulfide (II) is oxidized with hydrogen peroxide in the presence of an acid or with a peracid, e.g. m-chloroperoxybenzoic acid to yield sulfone (III). Other methods of oxidation are reported in references like Smith and March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Ed., Wiley Interscience, 2001. If sulfone (III) is an ester, it is further hydrolyzed to yield a carboxylic acid (IV, not shown) by basic hydrosolysis with a base like lithium, sodium, or potassium hydroxide, followed by acidic workup. Acid (IV) is then coupled to an amine to yield the final target product.

20

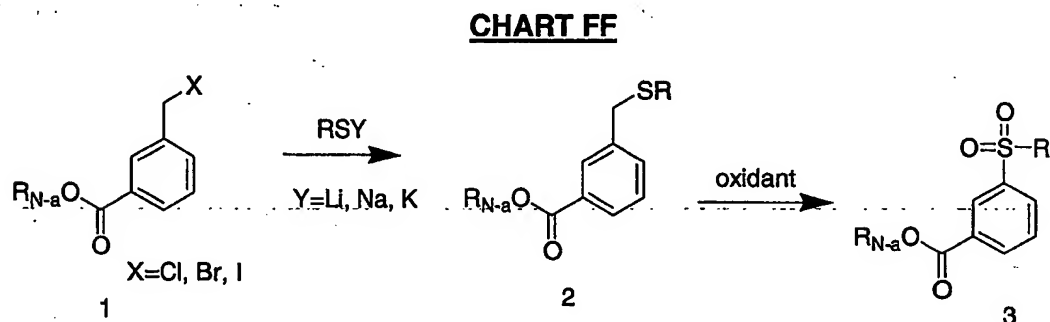


Chart FF. A halogenated benzyl-derivative of structure (1). (1) is reacted with thiolate, for example a lithium, sodium or potassium thiolate, in an organic solvent, for example THF, toluene, or acetonitrile, at temperatures ranging from room temperature to reflux, yielding a sulfanyl derivative of structure (2). (2) is peroxidated with an oxidant, for example hydrogen peroxide in the presence of an acid like acetic acid

or m-chloroperoxybenzoic acid, in an organic solvent like dichloromethane to yield methylene sulfone (3). Other methods of oxidation are reported in references like Smith and March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Ed., Wiley Interscience, 2001. If necessary, sulfone (3) is hydrolyzed to its acid derivative by methods known to those skilled in the art, or is used directly if already a carboxylic acid; coupling of said acid with amine yields the target product.

10

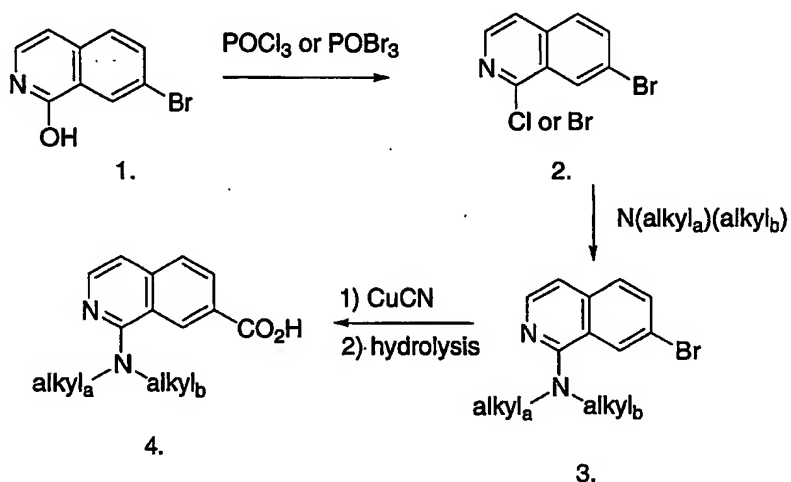
CHART GG

Chart GG. Isoquinoline (1) is reacted with phosphorus oxychloride or phosphorus oxybromide at temperatures ranging from room temperature to about 150 °C to yield halo-isoquinoline (2). Halo-isoquinoline (2) is reacted with an amine at temperatures ranging from room temperature to 200 °C to yield amino-isoquinoline (3). This reaction may be carried out in the presence of an organic solvent such as THF, acetonitrile, DMF, or NMP. Alternatively, the amine can be used as solvent, and a sealed reaction vessel may be used to contain volatile amine at high temperatures. Amino-isoquinoline (3) is reacted with copper (I) cyanide in an organic solvent, for example DMF or NMP (N-methylpyrrolidinone) at temperatures ranging from about 120 °C

to reflux, followed by hydrolysis with an aqueous acid, for example aqueous HCl, to yield isoquinoline carboxylic acid (4). Additional methods for converting amino-isoquinoline (3) to isoquinoline carboxylic acid (4) are known to those skilled in the art and include, for example, reacting (3) with carbon monoxide and an alcohol in the presence of a catalyst, for example a palladium catalyst such as palladium acetate or palladium(0) tetrakis(triphenylphosphine), and an additive, for example 1,1'-bis (diphenylphosphino) ferrocene or 1,3-bis (diphenylphosphino) propane, in an organic solvent, for example DMF or NMP, and in the presence of a base, for example a trialkylamine or aqueous sodium or potassium carbonate or sodium or potassium hydrogen carbonate, at temperatures ranging from about 50 to about 150 °C, followed by hydrolysis of the ester product to isoquinoline carboxylic acid (4). Isoquinoline carboxylic acid (4) is then coupled to an amine to yield the final target product.

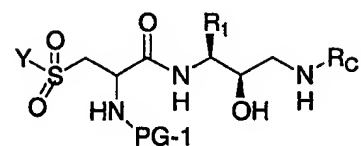
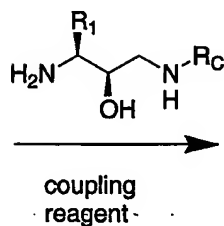
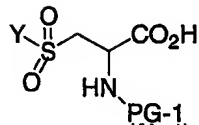
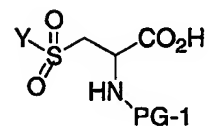
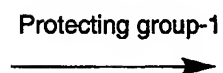
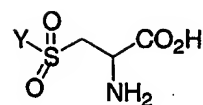
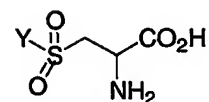
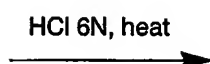
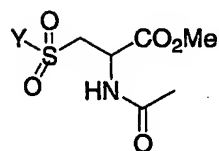
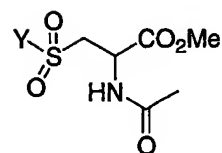
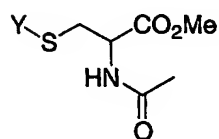
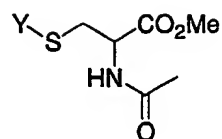
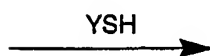
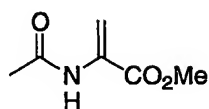
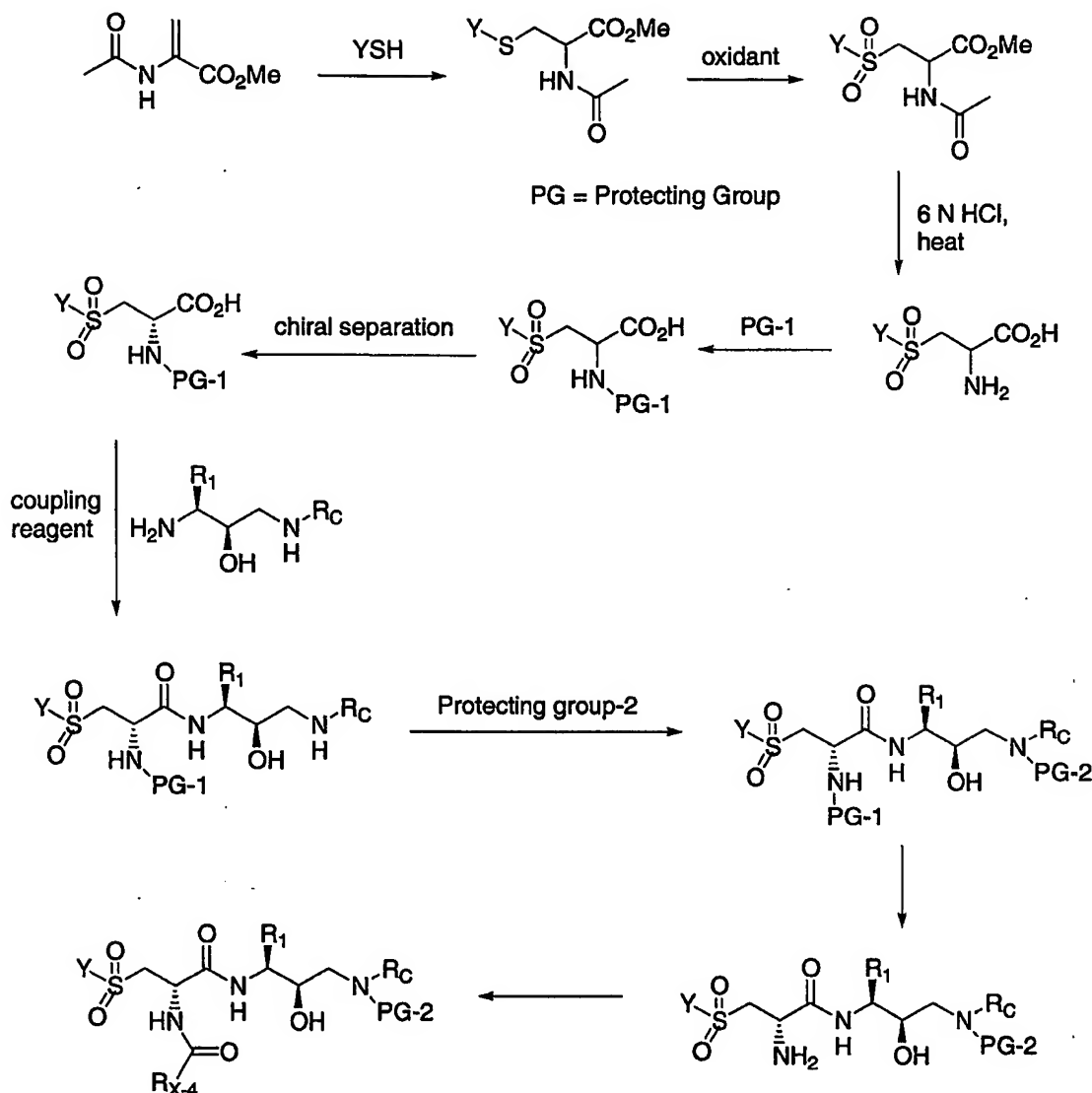
CHART HH

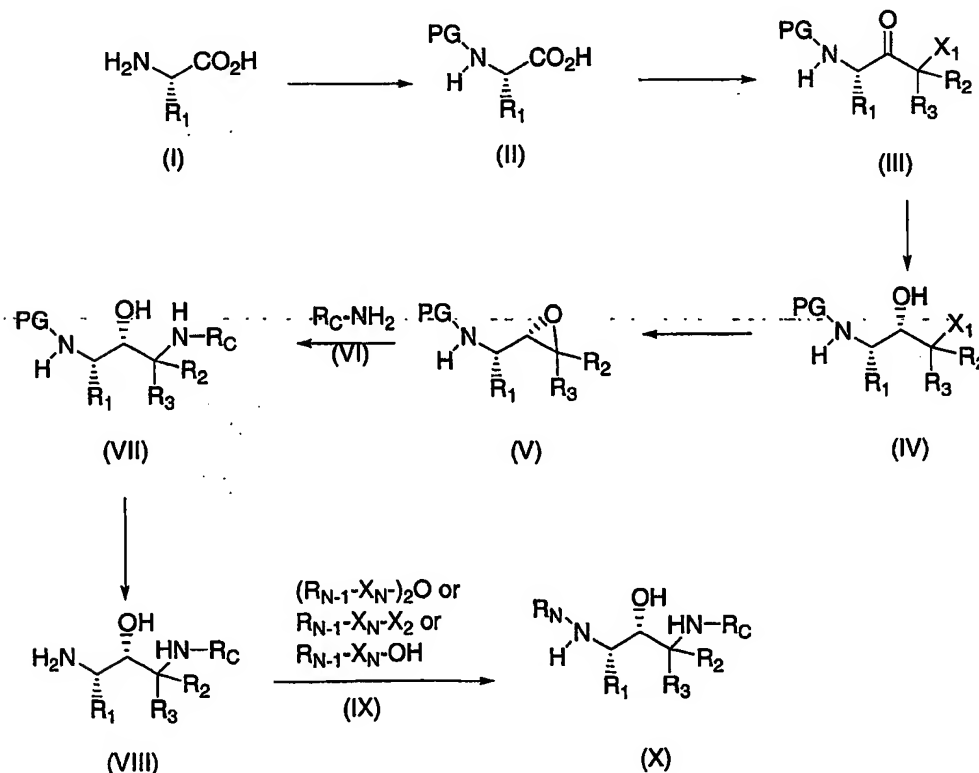
CHART II

Charts HH and II. Chart HH discloses the synthesis of a set of racemic α -amino sulfones while Chart II discloses the synthesis of the active enantiomer. The Michael addition of a thiol to a protected dehydroalanine methyl ester yields a sulfanyl intermediate. The sulfanyl derivative is peroxidated to the corresponding sulfone according to one of the above-mentioned methods. Hydrolysis of the ester and protecting group may be carried out with a strong aqueous acid, for example 6N HCl, or acetic acid, optionally at high temperature to yield the free amino acid salt. A protecting group for

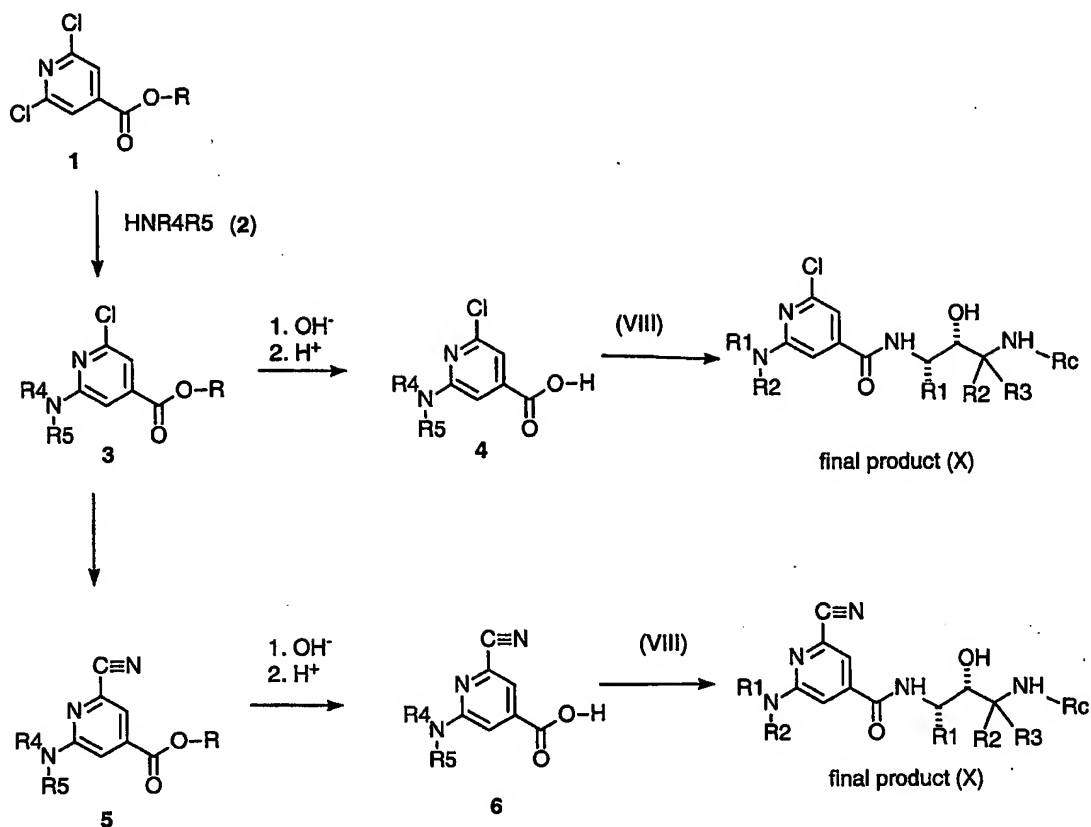
example Cbz or Boc, may be added to the amine group. Standard peptide coupling to the unprotected diamine preferentially affords the product with an unreacted N-R_C moiety which is then orthogonally protected to yield the diprotected diamine.

- 5 Selective removal of the R_N protecting group affords a free amine. This amine can be converted according one of the above-mentioned methods into amides, carbamates, .
- Alternatively, it may be reacted with an isocyanate to yield a urea, or with a sulfonyl chloride to yield a sulfonamide. The
- 10 removal of the R_C protecting yields the target compounds. Chart II is identical to chart HH with an additional isomer separation step which may be carried out chemically, enzymatically, or by chiral chromatography, yielding the single isomer acid which is transformed into the target
- 15 product as described above.

CHART JJ



ChartKK



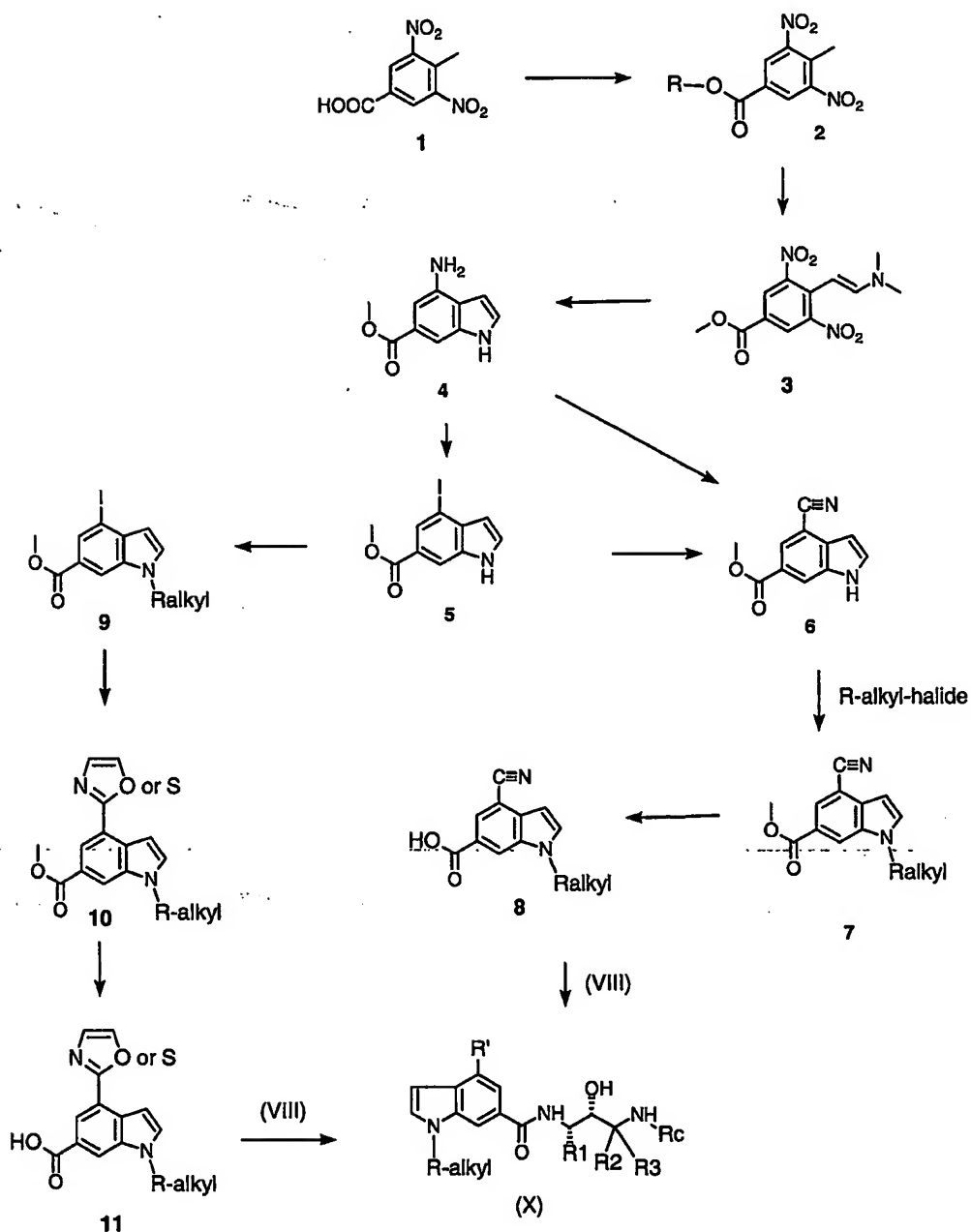
5 Pyridine 1 is reacted with an amine 2 in an organic solvent, for example THF, at reflux or by warming to a temperature ranging from about 80 °C to about 130 °C in a sealed vessel, to yield pyridine ester 3. Pyridine ester 3 is hydrolyzed using methods known to those skilled in the art to
 10 yield chloro-acid 4. Chloro-acid 4 is coupled to amine (VIII) using methods discussed above and known to those skilled in the art to yield final product (X).

Alternatively, ester pyridine 3 is cyanated as taught in Tet. Lett. 2000, 41, 3271 to yield nitrile ester 5. Additional
 15 methods of preparing nitrile ester 5 include but are not limited to treatment of ester pyridine 3 with copper cyanide in organic solvents, for example N-methylpyrrolidinone, DMF at temperatures ranging from about 80 °C to about 180 °C. The ester moiety of 5 is converted to acid 6 via methods known

to those skilled in the art. Acid 5 is then coupled to amine (VIII) using methods that are discussed above or known to those skilled in the art to give final product (X).

5

Chart LL



Dinitro acid **1** is esterified with an alcohol and an acid catalyst or by methods known to those skilled in the art to yield dinitro ester **2**. Dinitro ester **2** is reacted with a

protected aldehyde, for example an acetal or a ketal, in an organic solvent, for example toluene, at temperatures from about 50 to 150 °C and in the presence of an acid catalyst, for example concentrated sulfuric acid or sulfosalicylic acid, yielding dinitro amine 3. Dinitro amine 3 is treated with a palladium catalyst such as palladium on carbon in an organic solvent, for example methanol, ethanol, ethyl acetate, and acetonitrile, in the presence of an acid such as formic or acetic acid to yield amino-indole 4. Amino-indole 4 is reacted with sodium nitrite and aqueous hydrochloric or sulfuric acid, followed by potassium iodide, to give iodo-indole 5. Iodo-indole 5 is reacted with copper cyanide in an organic solvent, for example N-methylpyrrolidinone at temperatures from about 100 to about 200 °C to yield nitrile-indole 6. Nitrile-indole 6 is then alkylated with an alkyl halide, for example propyl or butyl iodide, bromide, or chloride in the presence of a base, for example sodium hydride or potassium tert-butoxide, preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO, preferably DMSO, at room temperature to 100 °C, to yield ester indole 7.

Alternatively, amino-indole 4 may be reacted with an aqueous mineral acid and sodium nitrite, followed by neutralization with a base, for example sodium bicarbonate, and then reacted with potassium cyanide and copper cyanide to yield nitrile-indole 6. Ester indole 7 is then hydrolyzed to indole acid 8 using methods known to those skilled in the art. Indole 8 is then coupled to amine (VIII) using methods known to those skilled in the art and previously disclosed in this document.

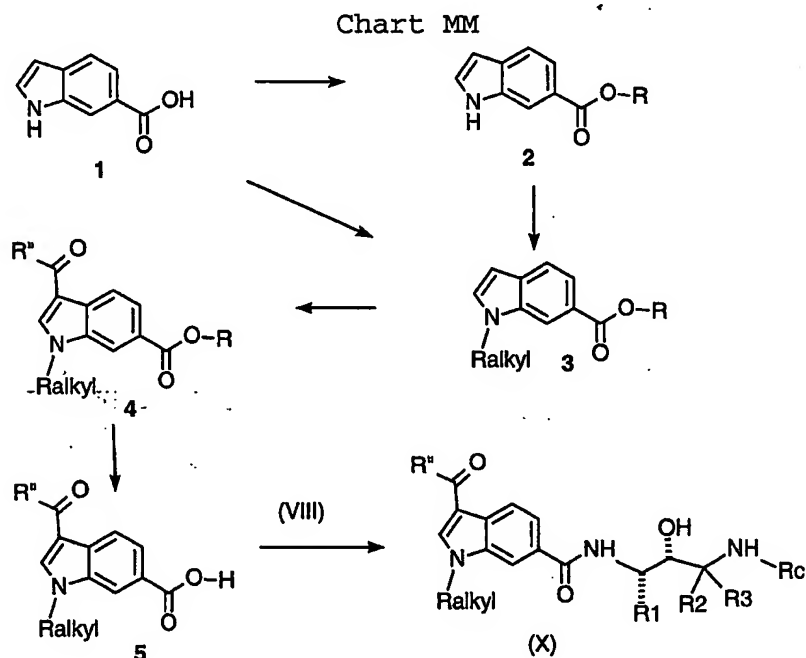
Alternatively, iodo indole 5 is reacted with an alkyl halide, for example as propyl or butyl iodide, bromide, or chloride in the presence of a base, for example sodium hydride or potassium tert-butoxide, more preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO,

preferably DMSO, at a temperature from room temperature to about 100 °C, to yield iodo alkyl **9**. An Oxazole or a thiazole in an organic solvent, for example dialkyl ether or THF, at a temperature from about 0 to about -78 °C is reacted with a

5 base, preferably butyl lithium and optionally left stirring for from about 15 to about 60 min. Zinc chloride is then added and the mixture is allowed to warm to 0-30 °C, at which time iodo alkyl **9** is added, followed by tetrakis triphenylphosphine palladium. The mixture is then optionally left stirring at a

10 temperature from room temperature to about 80 °C to yield oxazole/thiazole indole **10**. The hydrolysis of **10** by methods known to those skilled in the art yields oxazole/thiazole acid **11**. Oxazole/thiazole acid **11** is coupled to amine (VIII) using methods known to those skilled in the art.

15



20 Indole acid **1** is converted to indole ester **2** by methods known to those skilled in the art. Indole ester **2** is then alkylated with an alkyl halide, for example propyl or butyl iodide, bromide, or chloride, in the presence of a base, for

example sodium hydride or potassium tert-butoxide, preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO, preferably DMSO, at room temperature to about 100 °C to yield alkyl indole 3. Alternatively, indole acid 1 may be converted directly to alkyl indole 3 by reaction with an alkyl halide, for example propyl or butyl iodide, bromide, or chloride in the presence of a base, for example sodium hydride or potassium tert-butoxide, preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO, preferably DMSO at room temperature to about 100 °C. Alkyl indole 3 is then treated by the method disclosed in Org. Lett. (2000) 1485 and references cited therein, Tet. Lett. (1995) 4005 and references cited therein, and Org. Lett. (2001) 1005 and references cited therein to yield acylindole 4. Acylindole 4 is hydrolyzed to indole acid 5 using methods known to those skilled in the art, and indole acid 5 is coupled to amine (VIII) using methods known to those skilled in the art to yield (X).

20

BIOLOGICAL EXAMPLES

Example A

Enzyme Inhibition Assay

25 The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human

30

brain tissue as described in Sinha et.al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in
5 WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by
10 incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein
15 results in the generation of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW
20 751 mutation site.

Specific Assay Procedure:

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one
25 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of
30 each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-
35 bottom plate to which 30 microliters of ice-cold enzyme-

substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/well cold specimen diluent is added to stop the reaction and 20 microliters/well is transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hours incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control wells with no added compound. In this assay, the compounds of the invention exhibited an IC_{50} of less than or equal to 20 micromolar.

Example B

Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

Biotin-SEVNL-DAEFR[oregon green]KK

[SEQ ID NO: 1]

Biotin-SEVKM-DAEFR[oregon green]KK [SEQ ID NO: 2]
Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO: 3]
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF[oregon green]KK [SEQ ID NO: 4]

- 5 Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKA[oregon green]KK
[SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees C for 30 minutes. The
10 reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2%
15 DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example,
20 using a LJL Acquest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of
25 beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, compounds of the invention exhibited an IC50 of less than 20 micromolar.

Example C

30 **Beta-secretase inhibition: P26-P4'SW assay**

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, using the methods described, for example, in

published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLD AEF [SEQ ID NO: 6]

The P26-P1 standard has the sequence:

5 (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7]

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is
10 preferred. Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range
15 of the ELISA assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in
20 assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products...

25 Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5),
30 the samples are incubated with strepavidin-AP according to the manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with

streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

5

Example D**Assays using Synthetic Oligopeptide-Substrates**

Synthetic oligopeptides are prepared that incorporate the
10 known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage
15 products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

By way of example, one such peptide has the sequence SEVNL-
20 DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

.....These synthetic APP substrates are incubated in the
25 presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the compound inhibitor to control results provides a measure of the compound's inhibitory activity.

30

Example E**Inhibition of beta-secretase activity - cellular assay**

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation
5 Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et.al., 1992, Nature 360:672-674), as described in USPN 5,604,102.

The cells are incubated in the presence/absence of the
10 inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using
15 specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

20 **Example F**

Inhibition of Beta-Secretase in Animal Models of AD

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal
25 models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic
30 non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et.al., 1995, Nature 373:523-527 are useful to analyze *in vivo* suppression of A beta release in the presence of putative inhibitory

compounds. As described in USPN 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor preferably formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

Example G

Inhibition of A beta production in human patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

10 **Example H**

Prevention of A beta production in patients at risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor preferably formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

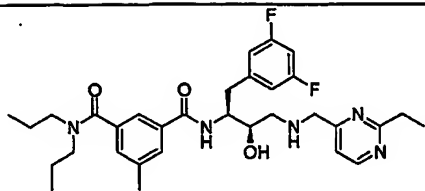
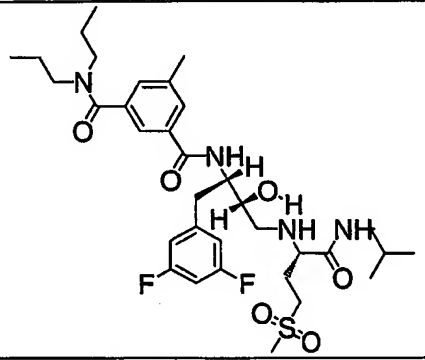
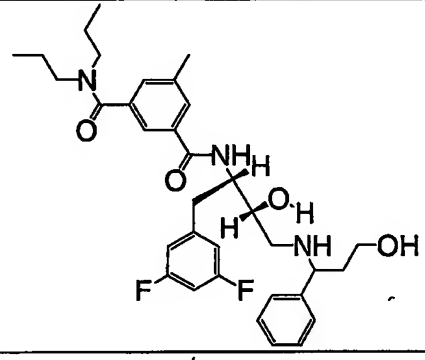
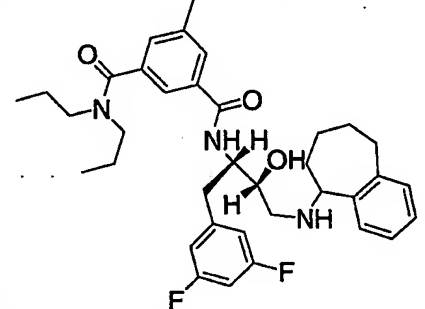
Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereby and should only be construed by interpretation of the scope of the appended claims.

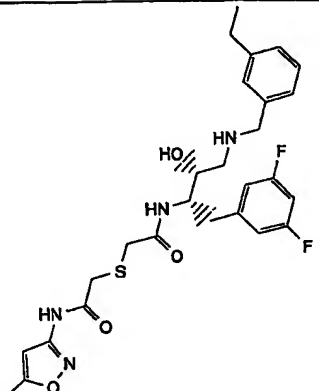
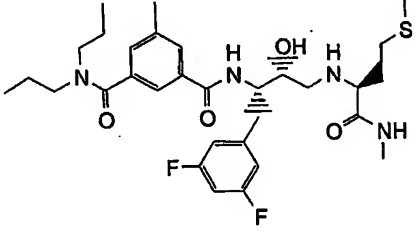
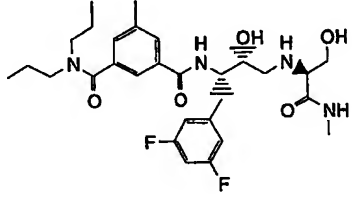
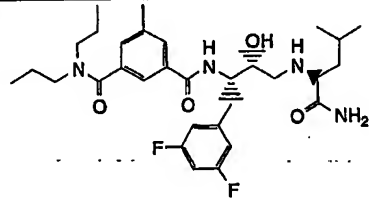
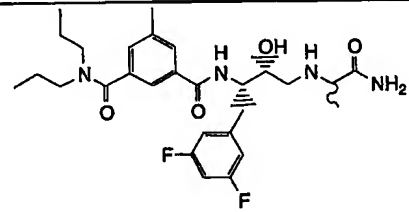
The following compounds were prepared using the above described methodology.

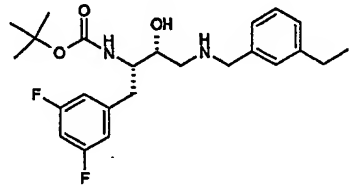
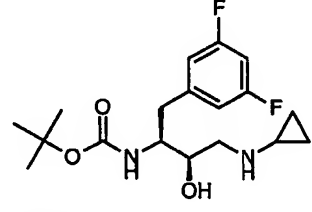
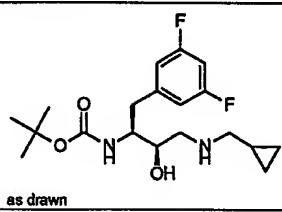
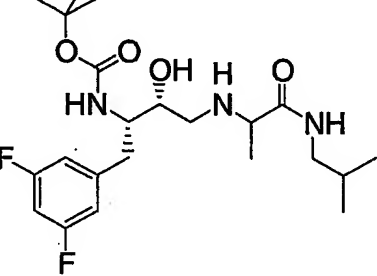
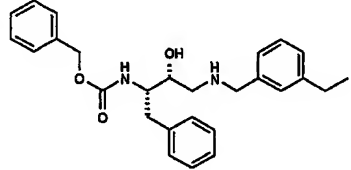
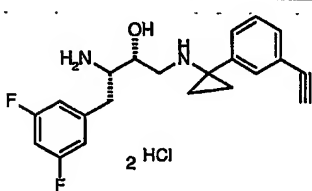
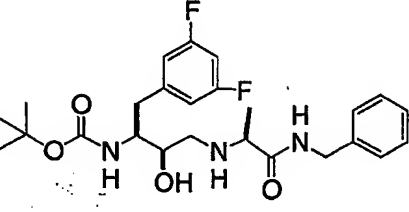
Example	Structure	Compound Name(s)	Mass Spec +H ⁺
3552		N'-[(1S,2S)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	552.2
3553		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N,N-dipropylisophthalamide	590.3
3554		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-[(1E)-prop-1-en-1-yl]benzyl)amino]propyl]-5-methyl-N,N-dipropylisophthalamide	592.3
3555		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N,N-dipropylisophthalamide	647.2
3556		methyl (3-[[[(2R,3S)-4-(3,5-difluorophenyl)-3-[[3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoyl]amino]-2-hydroxybutyl]amino]methyl]phenyl)methylcarbamate	692.2

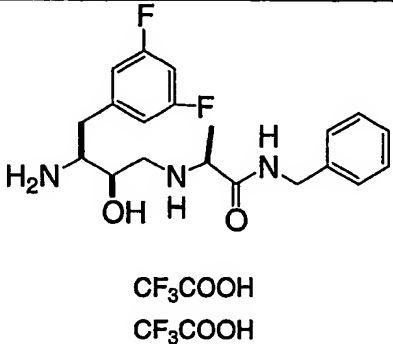
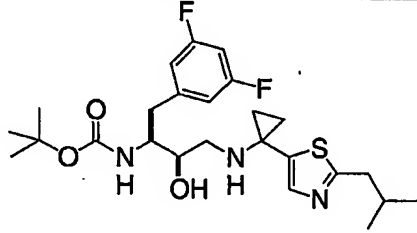
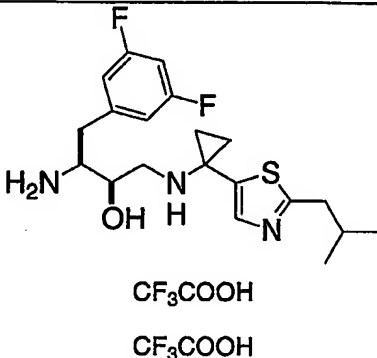
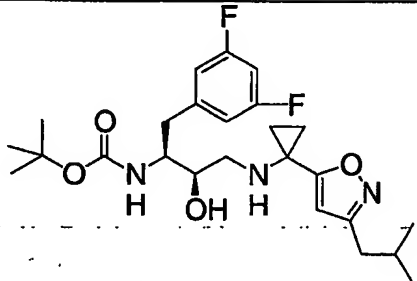
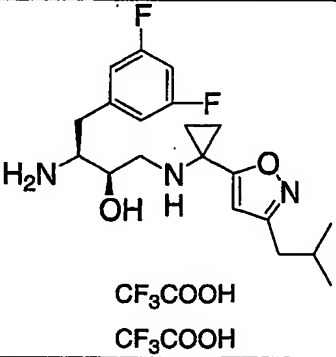
3557		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(methylsulfonyl)amino]benzyl}amino)propyl]-5-(1,3-oxazol-2-yl)-N,N-dipropylisophthalamide	698.2
3558		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl]-N,N-dipropylpyridine-3,5-dicarboxamide	MS 582 (M+H).
3559		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N,N-dipropylpyridine-3,5-dicarboxamide 1-oxide	MS 584 (M+H).
3560		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]-5-ethynyl-N,N-dipropylisophthalamide	MS 587 (M+H).
3561		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl]-6-methyl-N²,N²-dipropylpyridine-2,4-dicarboxamide	MS 595 (M+H).
3562		N'-[(1S,2R)-3-[(2-tert-butylpyrimidin-4-yl)methyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	610

3563		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-(((2-ethylpyrimidin-4-yl)methyl)amino)-2-hydroxypropyl)-5-methyl-N,N-dipropylisophthalamide	583 605 (M+Na)
3564		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(((1S)-1-((isobutylamino)carbamoyl)-3-(methylsulfonyl)propyl)amino)propyl)-5-methyl-N,N-dipropylisophthalamide	681.3
3565		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-hydroxy-1-phenylpropyl)amino)propyl)-5-methyl-N,N-dipropylisophthalamide	596.3
3566		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ylamino)propyl)-5-methyl-N,N-dipropylisophthalamide	606.3

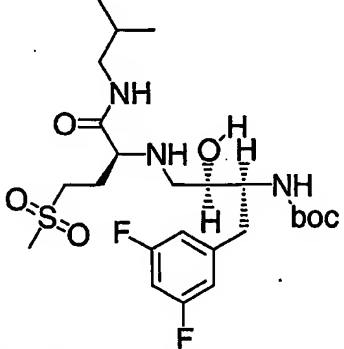
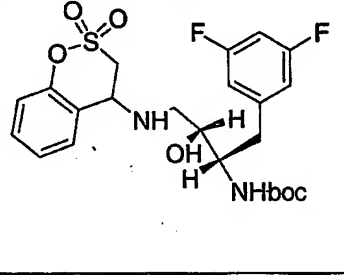
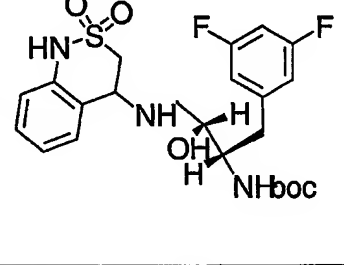
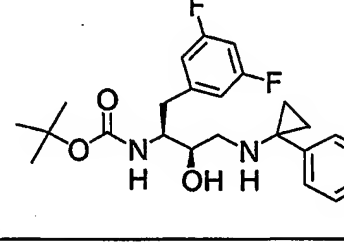
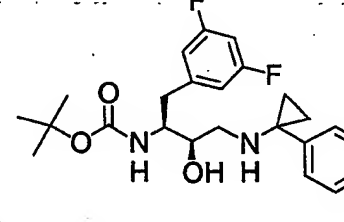
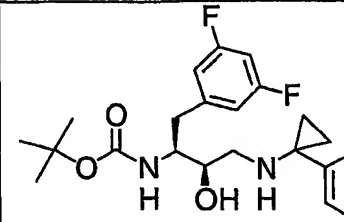
3567		N'-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide	Mass spec (CI) MH+-OMe-tetraline 462.2
3568		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide	Mass spec (CI) MH+-OMe-tetraline 462.2
3569		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[(1S)-2-oxo-1-methyl-2-(methylamino)ethyl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide	547.4
3570		N'-[[(1S,2R)-3-[[(1S)-1-benzyl-2-oxo-2-(methylamino)ethyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3571		N'-{ (1S,2R)-1-(3,5-difluorobenzyl)-3-[[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N^2-{oxo[3-(trifluoromethyl)phenyl]methyl}glycinamide	

3572		2-{{2-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-2-oxoethyl]thio}-N-(5-methylisoxazol-3-yl)acetamide	
3573		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(1R)-1-oxo(methylamino)methyl]-3-(methylthio)propyl]amino)propyl)-5-methyl-N,N-dipropylisophthalamide	
3574		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(1R)-1-(hydroxymethyl)-2-oxo-2-(methylamino)ethyl]amino)propyl)-5-methyl-N,N-dipropylisophthalamide	
3575		N'-[(1S,2R)-3-((1S)-1-[amino(oxo)methyl]-3-methylbutyl)amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3576		N'-[(1S,2R)-3-[(2-amino-2-oxo-1-methylethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	

3577		tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropylcarbamate	
3578	 as drawn	tert-butyl (1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate	
3579	 as drawn	tert-butyl (1S,2R)-3-[(cyclopropylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate	
3580		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-oxo-2-(isobutylamino)-1-methylethyl]amino]propyl)carbamate	416.1
3581		benzyl (1S,2R)-1-benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropylcarbamate	
3582	 2 HCl	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[[1-(3-ethynylphenyl)cyclopropyl]amino]butan-2-ol hydrochloride	357.2
3583		tert-butyl [(1S,2R)-3-[[[(1S)-2-(benzylamino)-2-oxo-1-methylethyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]carbamate	478.1

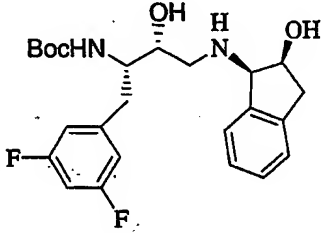
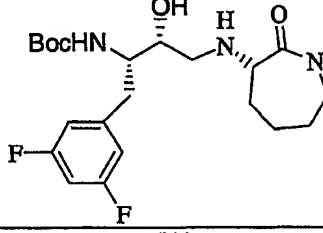
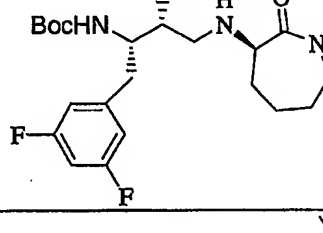
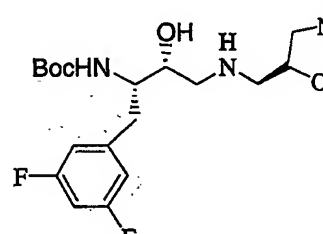
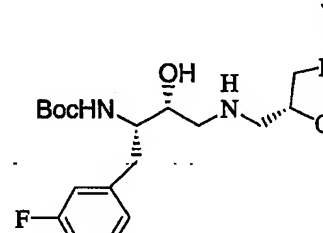
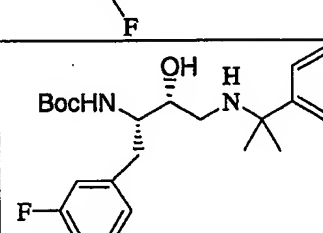
3584	 <p>CF₃COOH CF₃COOH</p>	N ² -[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]-N ¹ -benzyl-L-alaninamide bis(trifluoroacetate) (salt)	
3585	 <p>CF₃COOH</p>	tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino)propyl)carbamate	496.2
3586	 <p>CF₃COOH CF₃COOH</p>	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-([1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino)butan-2-ol bis(trifluoroacetate) (salt)	
3587	 <p>CF₃COOH</p>	tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino)propyl)carbamate	480.2
3588	 <p>CF₃COOH CF₃COOH</p>	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-([1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino)butan-2-ol bis(trifluoroacetate) (salt)	

3589		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-3-(((2-ethylpyrimidin-4-yl)methyl)amino)-2-hydroxypropyl) carbamate	437.3
3590		(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(((2-ethylpyrimidin-4-yl)methyl)amino)butan-2-ol bis(trifluoroacetate) (salt)	
3591		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino)propyl) carbamate	477.5
3592		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)amino)propyl) carbamate	461.2
3593		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-hydroxy-1-phenylpropyl)amino)propyl) carbamate	451.2
3594		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(((1S)-1-oxo(isobutylamino)methyl)-3-(methylthio)propyl)amino)propyl) carbamate	504.3

3595		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1S)-1-((isobutylamino)carbonyl)-3-(methylsulfonyl)propyl)amino)propyl)carbamate	536.2
3596		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiazin-4-yl)amino]-2-hydroxypropyl)carbamate	499.1
3597		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl)amino]-2-hydroxypropyl)carbamate	498.1
3598		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)carbamate	461.3
3599		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)carbamate	457.2
3600		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-(3-methylphenyl)cyclopropyl]amino)propyl)carbamate	447.2

3601		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-(3-iodophenyl)cyclopropyl]amino)propyl)carbamate	558.4
3602		tert-butyl [(1S,2R)-3-([3-(cyclopropylamino)benzyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]carbamate	462.2
3603		methyl 3-([(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino)methyl)benzoate	465.1
3604		methyl [3-([(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino)methyl]phenyl]carbamate	480.1
3605		methyl [3-([(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino)methyl]phenyl]methylcarbamate	494.1
3606		tert-butyl [(1S,2R)-1-(3,5-difluorobenzyl)-3-([3-[(dimethylamino)sulfonyl]benzyl]amino)-2-hydroxypropyl]carbamate	514.1
3607		tert-butyl [(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-[(methylsulfonyl)aminobenzyl]amino)propyl]carbamate	500.1

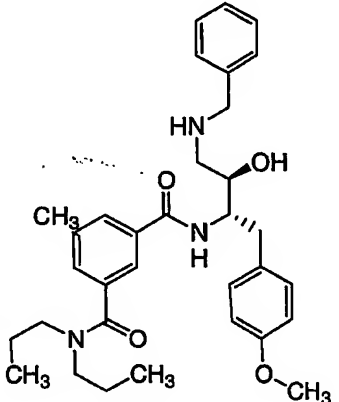
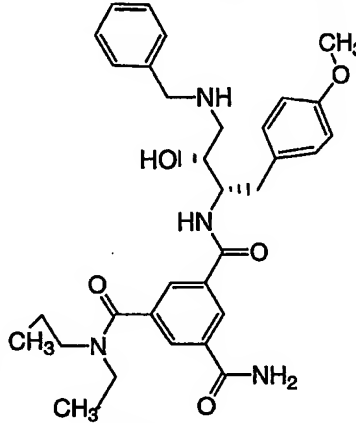
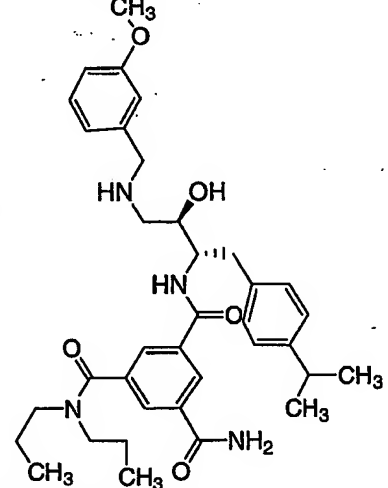
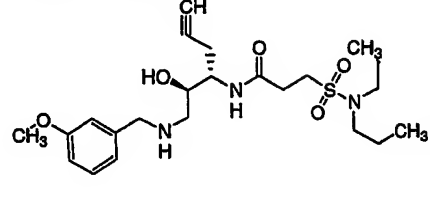
3608		tert-butyl [(1S,2R)-3-[(3-cyanobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl] carbamate	432.1
3609		3-({[(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}methyl)phenyl dimethylcarbamate	494.1
3610		tert-butyl [(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl][3-(ethylthio)benzyl] carbamate	612.3
3611		tert-butyl {(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1R)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl} carbamate	433.2
3612		tert-butyl {(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1S)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl} carbamate	433.2
3613		tert-butyl {(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}propyl carbamate	449.2

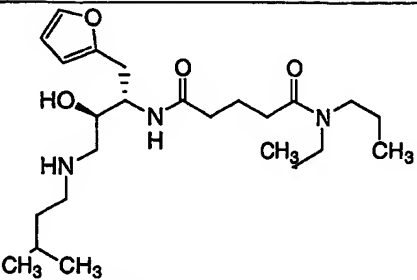
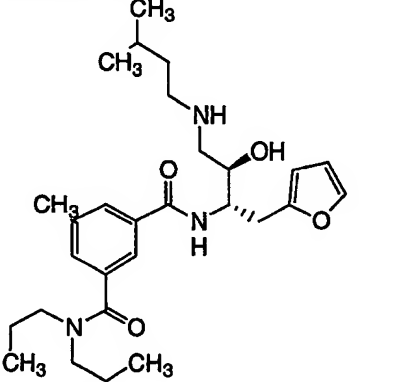
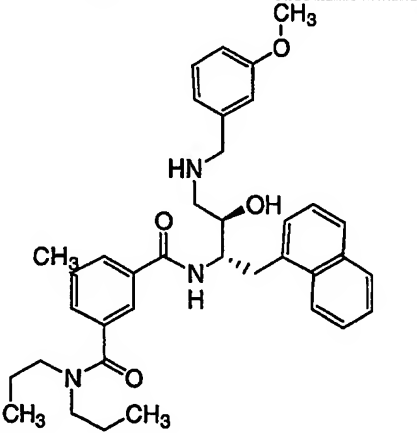
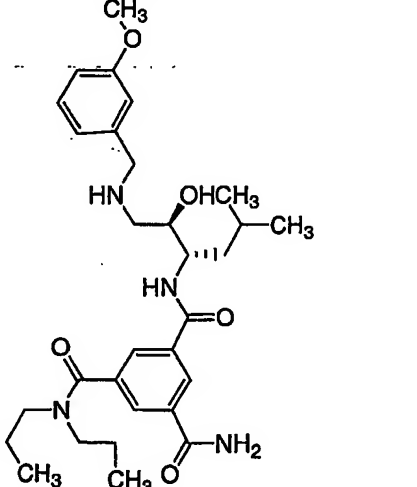
3614		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)propyl)carbamate	449.4
3615		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3S)-2-oxoazepan-3-yl)amino)propyl)carbamate	428.2
3616		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3R)-2-oxoazepan-3-yl)amino)propyl)carbamate	428.2
3617		tert-butyl [(1S,2R)-1-(3,5-difluorobenzyl)-3-(((5S)-3-ethyl-2-oxo-1,3-oxazolidin-5-yl)methyl)amino)-2-hydroxypropyl]carbamate	444.2
3618		tert-butyl [(1S,2R)-1-(3,5-difluorobenzyl)-3-(((5R)-3-ethyl-2-oxo-1,3-oxazolidin-5-yl)methyl)amino)-2-hydroxypropyl]carbamate	444.2
3619		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)-1-methylethyl]amino)-2-hydroxypropyl)carbamate	475.2

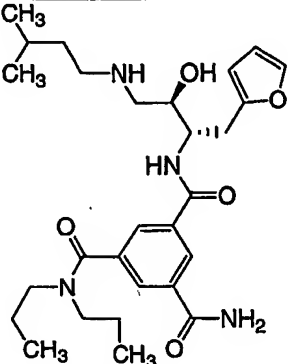
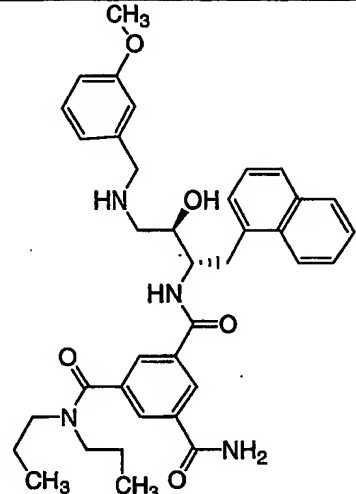
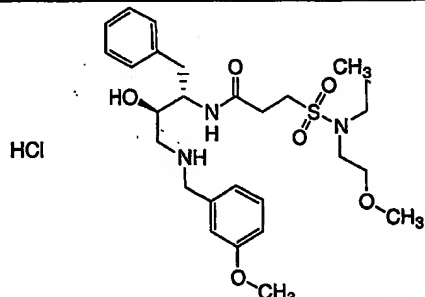
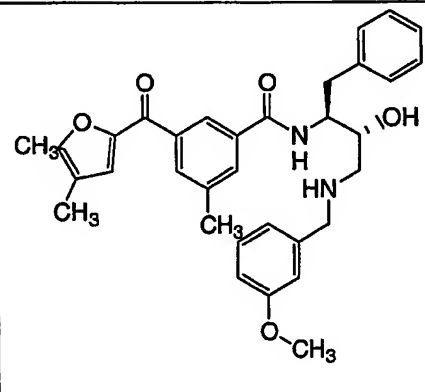
3620		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-naphthylmethyl)amino]propyl)carbamate	463.3
3621		tert-butyl ((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-oxo-2-(isobutylamino)-1,1-dimethylethyl]amino]propyl)carbamate	458.2
3622		tert-butyl [(1S,2R)-3-[(benzyloxy)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]carbamate	423.1
3623		tert-butyl 4-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino]carbonyl]piperidine-1-carboxylate trifluoroacetate	
3624		N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-fluoro-1-naphthamide	
3625		N-[(1S,2R)-1-benzyl-3-(2-butyryl-1-ethylhydrazino)-2-hydroxypropyl]-2-(3-methylisoxazol-5-yl)acetamide	

3626		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-hexyl-N,5-dimethylisophthalamide	
3627		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzoyl)amino]propyl}-5-methyl-N,N-dipropylisophthalamide	
3628		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-imidazole-2-carboxamide	
3629		N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,3-dimethyl-N²,N²-dipropylcyclopropane-1,2-dicarboxamide	
3630		tert-butyl 2-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropylamino]carbonyl-1-methyl-1H-imidazol-4-ylcarbamate	
3631		N⁵-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,2-dimethyl-N¹,N¹-dipropylpentanediamide	

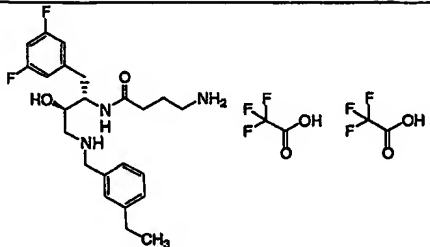
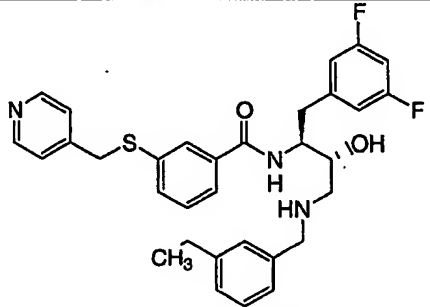
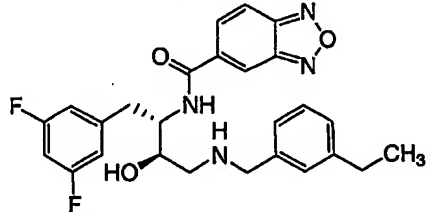
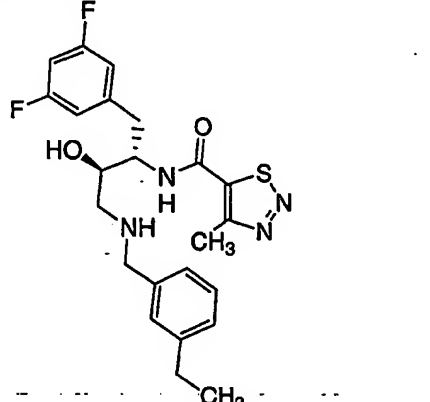
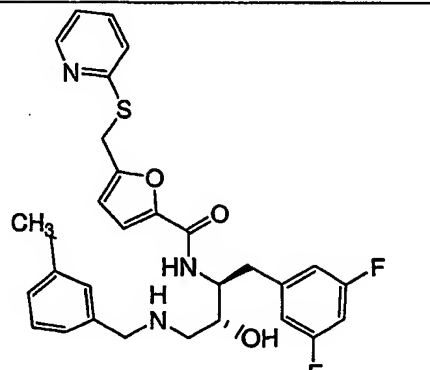
3632		N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(2-morpholin-4-ylethyl)amino]propyl]-2-(4-chlorophenoxy)-2-methylpropanamide compound with methyl hydroperoxide (1:2)	
3633		N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-4-fluoro-1-naphthamide	
3634		3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]propanamide	
3635		3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]propanamide	
3636		N ¹ -[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N ⁵ ,N ⁵ -dipropylpentanediamide	

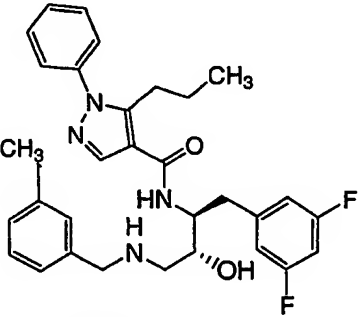
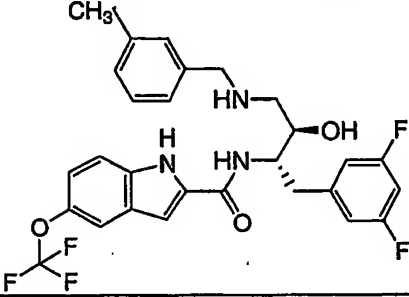
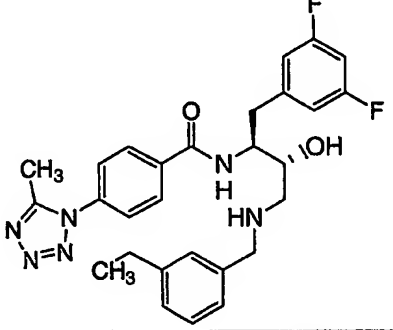
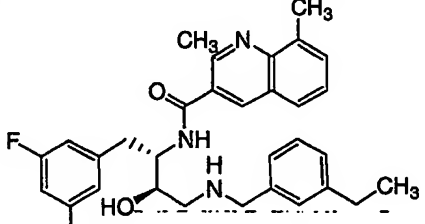
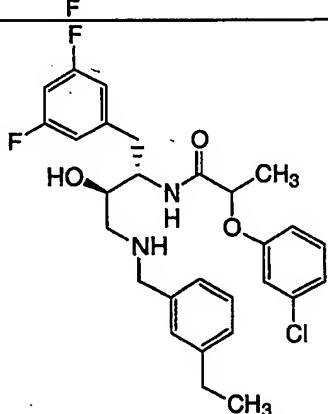
3637		N¹-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-5-methyl-N³,N³-dipropylisophthalamide	
3638		N¹-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-N³,N³-dipropylbenzene-1,3,5-tricarboxamide	
3639		N¹-[(1S,2R)-2-hydroxy-1-(4-isopropylbenzyl)-3-[(3-methoxybenzyl)amino]propyl]-N³,N³-dipropylbenzene-1,3,5-tricarboxamide	
3640		3-[(dipropylamino)sulfonyl]-N-[(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]but-3-ynyl]propanamide	

3641		N¹-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N⁵,N⁵-dipropylpentanediamide	
3642		N¹-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N³,N³-dipropylisophthalamide	
3643		N¹-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1-naphthylmethyl)propyl]-5-methyl-N³,N³-dipropylisophthalamide	
3644		N¹-[(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]-3-methylbutyl]-N³,N³-dipropylbenzene-1,3,5-tricarboxamide	

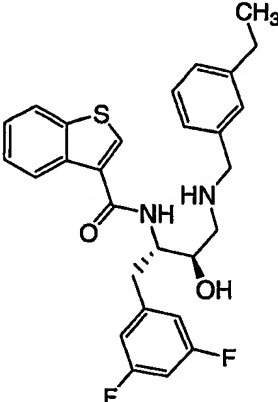
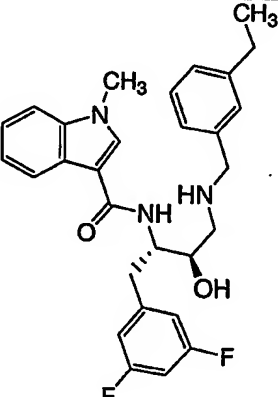
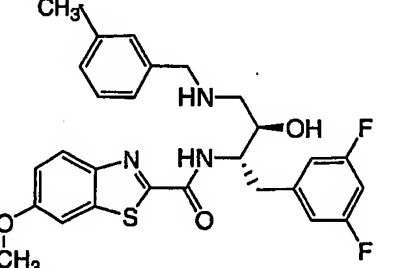
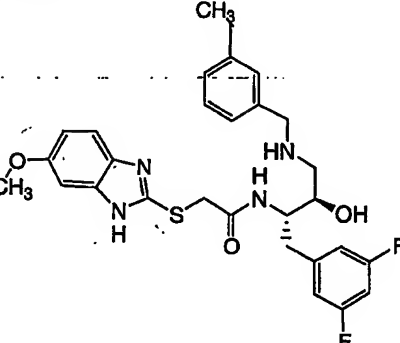
3645		N¹-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N³,N³-dipropylbenzene-1,3,5-tricarboxamide	
3646		N¹-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1-naphthylmethyl)propyl]-N³,N³-dipropylbenzene-1,3,5-tricarboxamide	
3647		N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(2-methoxyethyl)(propyl)amino]sulfonylpropanamide hydrochloride	
3648		N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-(4,5-dimethyl-2-furoyl)-5-methylbenzamide	

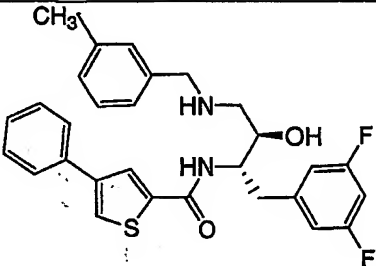
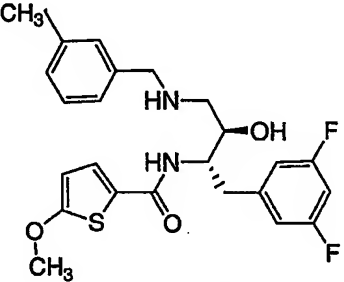
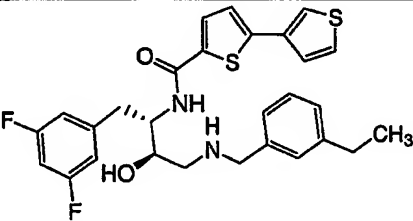
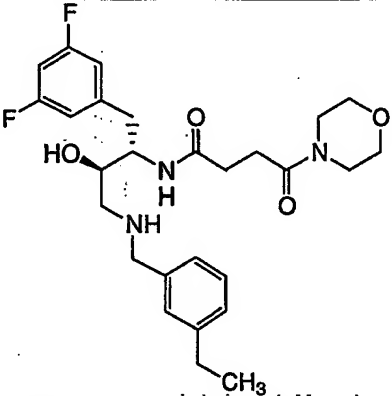
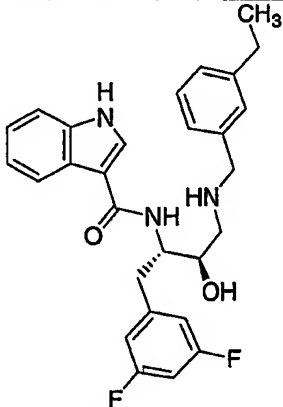
3649		3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]propanamide	
3650		1,3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-5-hydroxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]propanamide	
3651		N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-1,3-benzothiazole-2-carboxamide	
3652		N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-5-(2,5-dimethylphenoxy)-2,2-dimethylpentanamide	
3653		N-[(1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-(isopentylsulfonyl)propanamide trifluoroacetate	
3654		N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-hydroxy-5-methylbenzamide	471.4

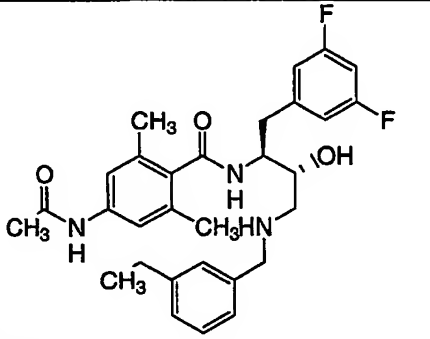
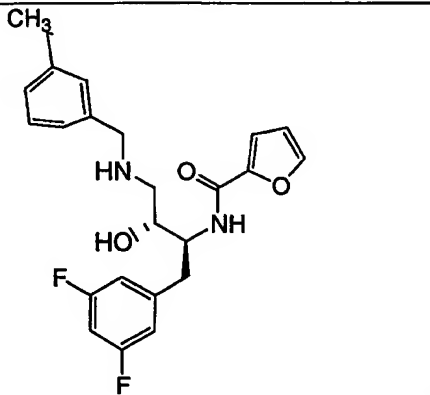
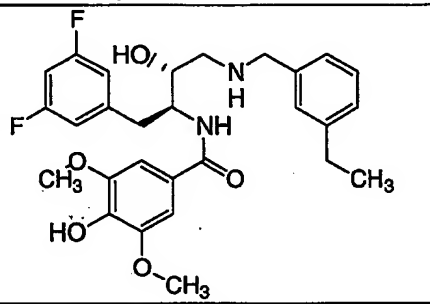
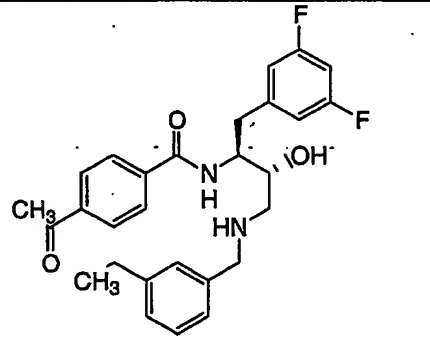
3655		4-amino-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)butanamide bis(trifluoroacetate)	
3656		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((pyridin-4-ylmethyl)thio)benzamide	
3657		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2,1,3-benzoxadiazole-5-carboxamide	
3658		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide	
3659		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-((pyridin-2-ylthio)methyl)-2-furamide	

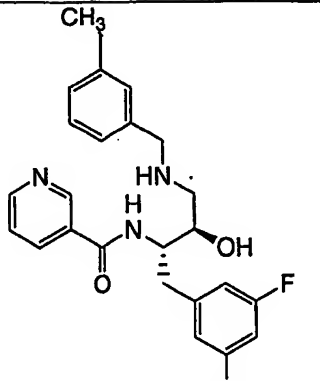
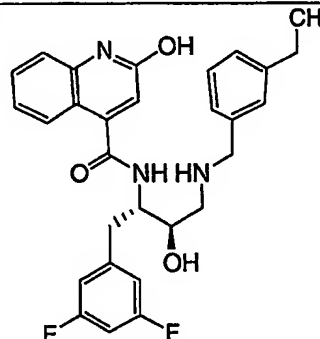
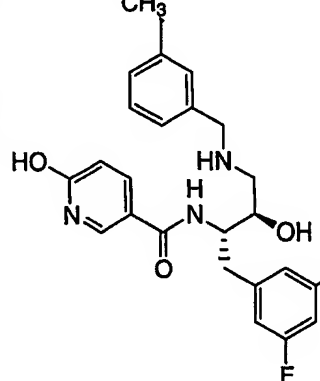
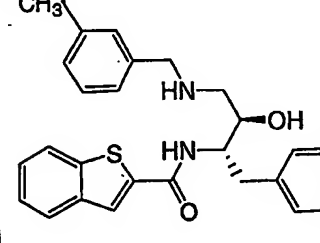
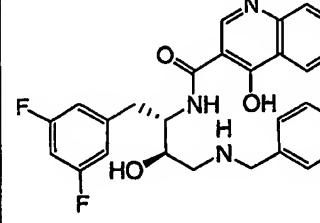
3660		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-phenyl-5-propyl-1H-pyrazole-4-carboxamide	
3661		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(trifluoromethoxy)-1H-indole-2-carboxamide	
3662		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(5-methyl-1H-tetrazol-1-yl)benzamide	
3663		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,8-dimethylquinoline-3-carboxamide	
3664		2-(3-chlorophenoxy)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)propanamide	

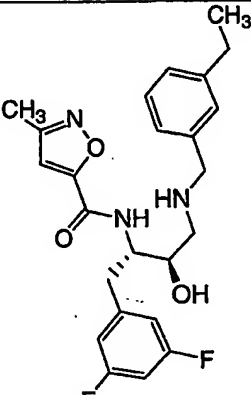
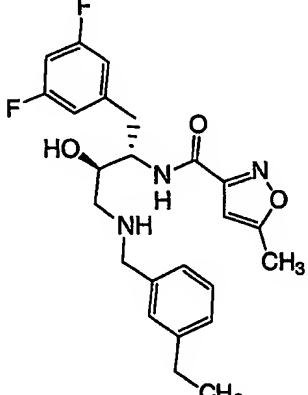
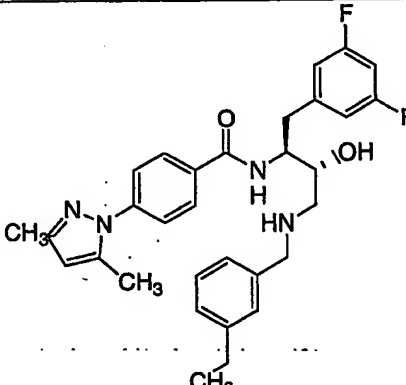
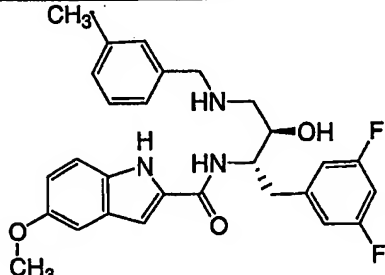
3665		2-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1H-tetrazol-1-yl)benzamide	
3666		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[5-(2-methylphenyl)-2H-tetrazol-2-yl]acetamide	
3667		3-(1,3-benzoxazol-2-ylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)propanamide	
3668		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-6-methylquinoline-4-carboxamide	
3669		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-propylpyrazine-2-carboxamide 4-oxide	

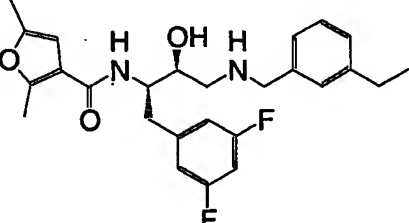
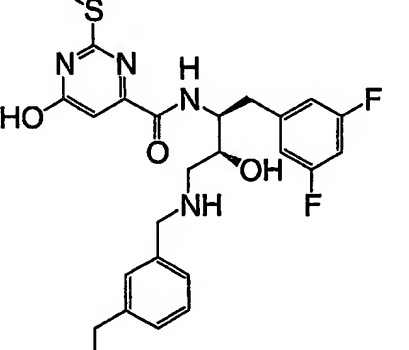
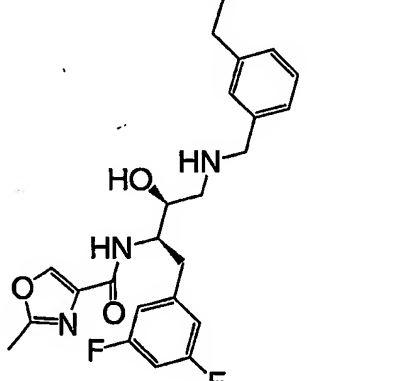
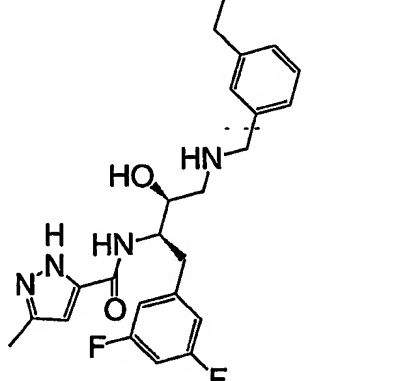
3670		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-benzothiophene-3-carboxamide	
3671		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-methyl-1H-indole-3-carboxamide	
3672		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-6-methoxy-1,3-benzothiazole-2-carboxamide	
3673		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((6-methoxy-1H-benzimidazol-2-yl)thio)acetamide	

3674		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-phenylthiophene-2-carboxamide	
3675		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-methoxythiophene-2-carboxamide	
3676		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2,3'-bithiophene-5-carboxamide	
3677		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-morpholin-4-yl-4-oxobutanamide	
3678		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indole-3-carboxamide	

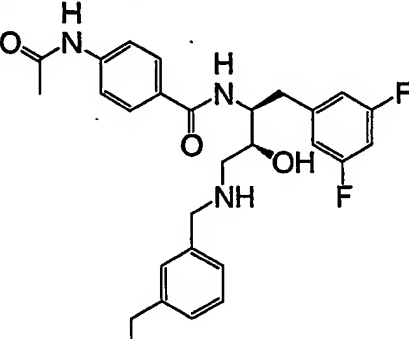
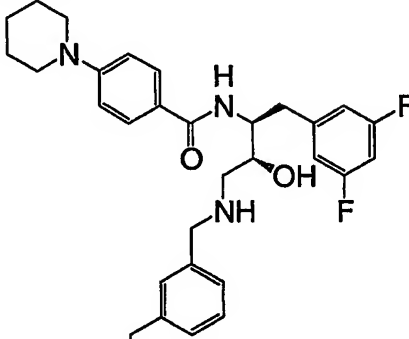
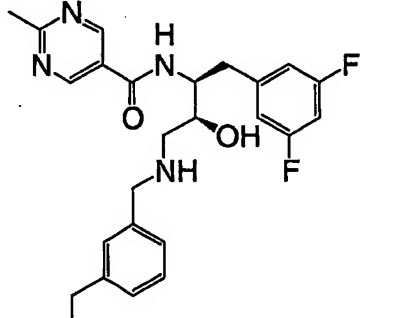
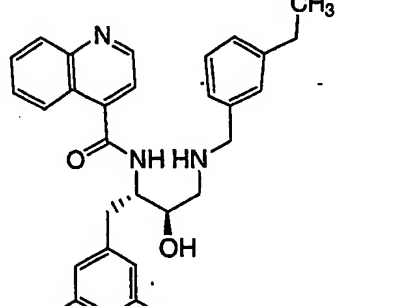
3679		4-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,6-dimethylbenzamide	
3680		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-furamide	
3681		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxy-3,5-dimethoxybenzamide	
3682		4-acetyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide	

3683		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)nicotinamide	
3684		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxyquinoline-4-carboxamide	
3685		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-hydroxynicotinamide	
3686		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-benzothiophene-2-carboxamide	
3687		7-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxyquinoline-3-carboxamide	

3688		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methylisoxazole-5-carboxamide	
3689		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methylisoxazole-3-carboxamide	
3690		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,5-dimethyl-1H-pyrazol-1-yl)benzamide	
3691		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methoxy-1H-indole-2-carboxamide	

3692		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2,5-dimethyl-3-furamide	
3693		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-6-hydroxy-2-(methylthio)pyrimidine-4-carboxamide	
3694		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-methyl-1,3-oxazole-4-carboxamide	
3695		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-methyl-1H-pyrazole-5-carboxamide	

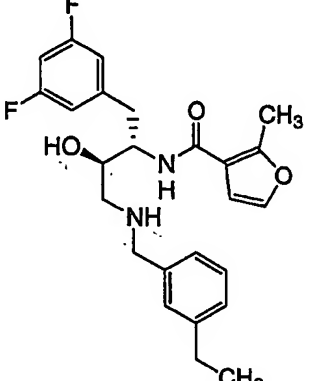
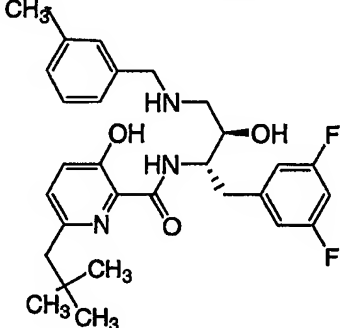
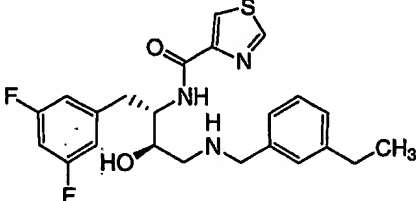
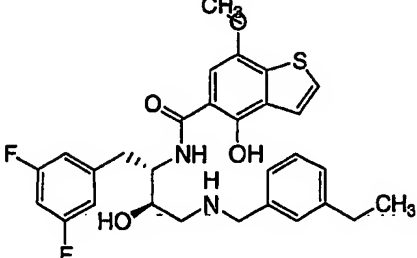
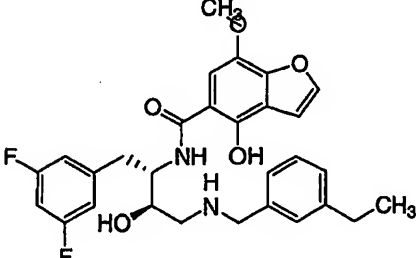
3696		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)thiophene-3-carboxamide	
3697		6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indole-2-carboxamide	
3698		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1H-indole-5-carboxamide	
3699		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-methyl-1,3-oxazole-5-carboxamide	
3700		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-methoxybenzamide	

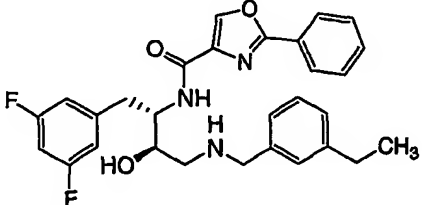
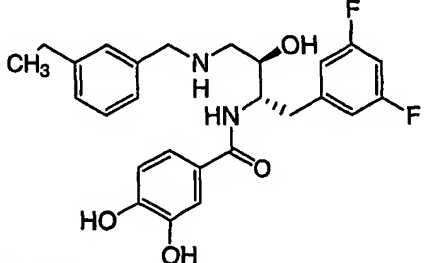
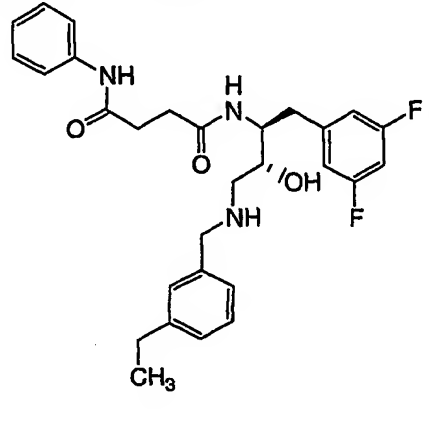
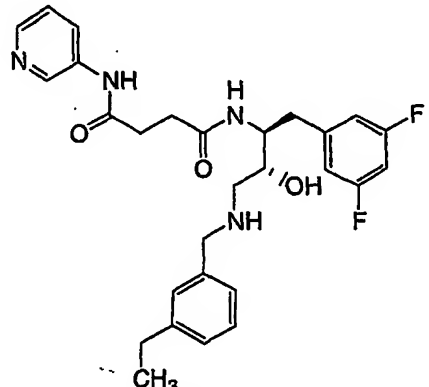
3701		4-(acetylamino)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}benzami de	
3702		N-((1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-4- piperidin-1- ylbenzamide	
3703		N-((1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-2- methylpyrimidine-5- carboxamide	
3704		N-((1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)quino line-4-carboxamide	

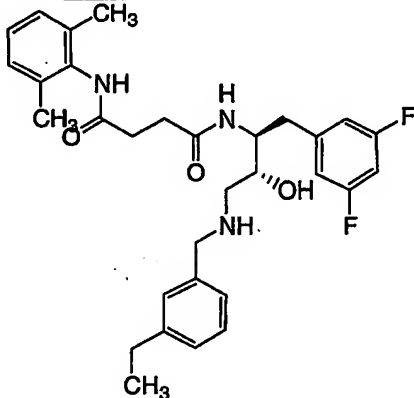
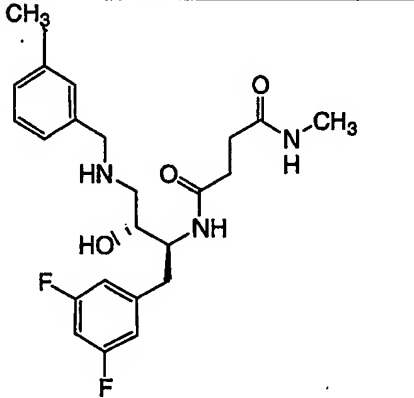
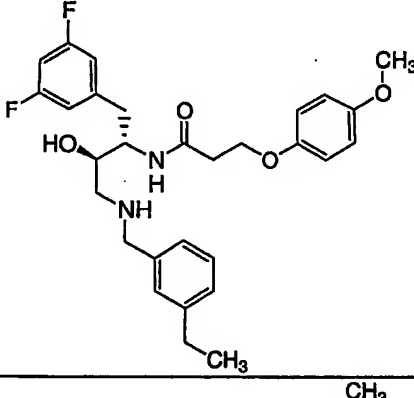
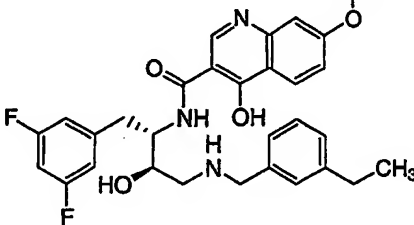
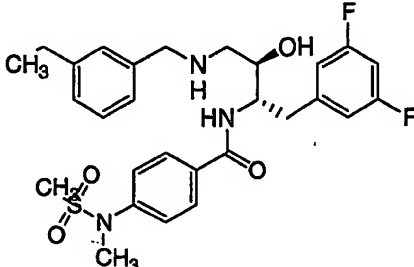
3705		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylimidazo[1,2-a]pyridine-7-carboxamide	
3706		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-hydroxy-4-methylpyridine-2-carboxamide	
3707		N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N^4,N^4-diphenylsuccinamide	
3708		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[ethyl(methyl)amino]-4-hydroxypyrimidine-5-carboxamide	
3709		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,8-dihydroxyquinoline-2-carboxamide	

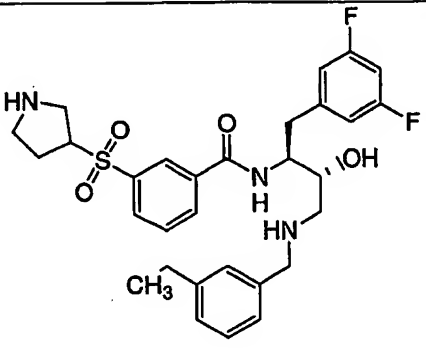
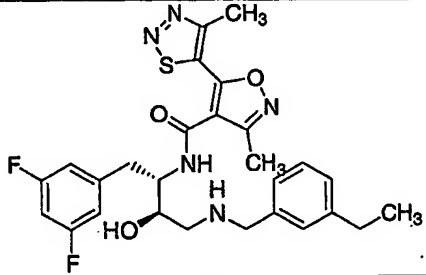
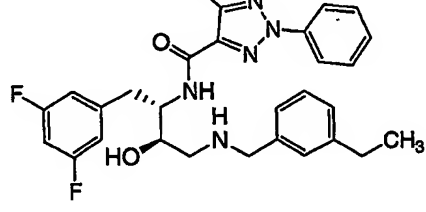
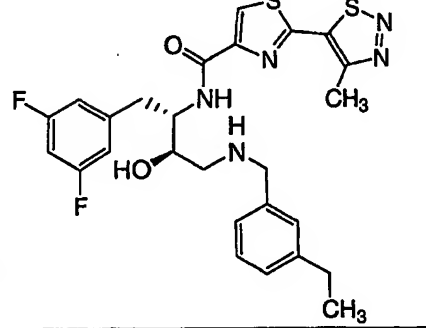
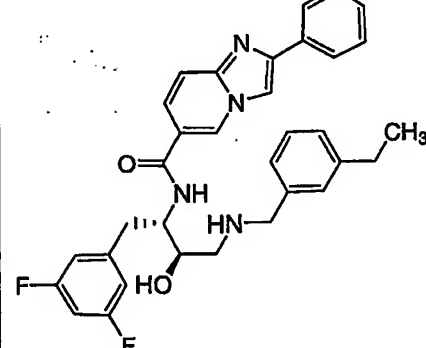
3710		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-benzofuran-2-carboxamide	
3711		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-ethyl-1H-indole-2-carboxamide	
3712		2-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,5-dimethylthiophene-3-carboxamide	
3713		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxyquinoxaline-2-carboxamide	
3714		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indazole-3-carboxamide	

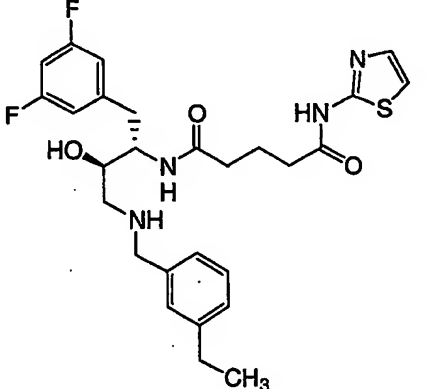
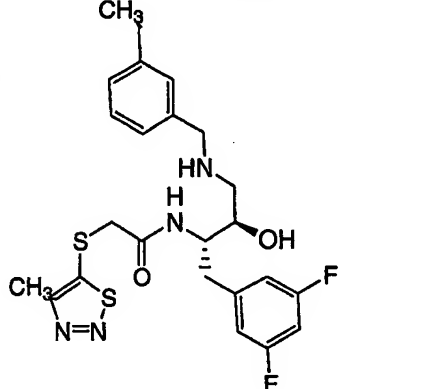
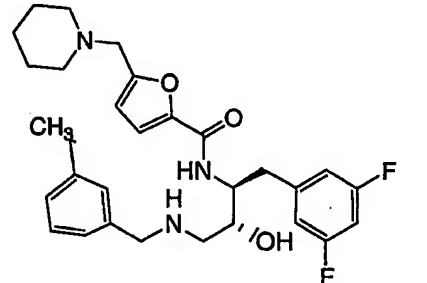
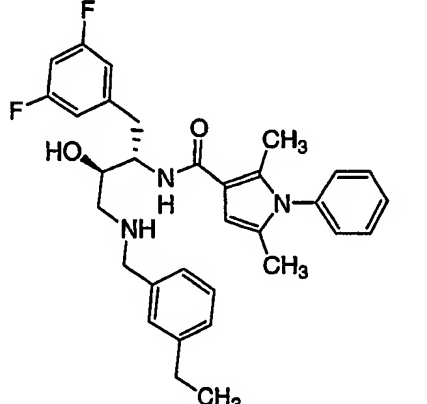
3715		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-2-phenyl-1,3-oxazole-4-carboxamide	
3716		4-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methylquinoline-2-carboxamide	
3717		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²,N²-dimethylphthalamide	
3718		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thiophene-2-carboxamide	
3719		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-furamide	

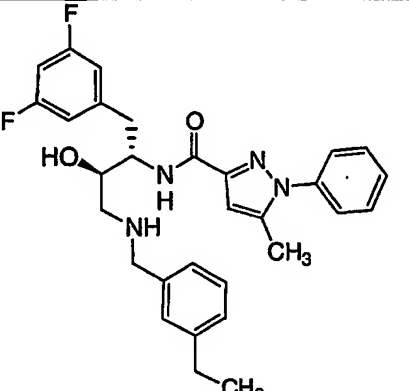
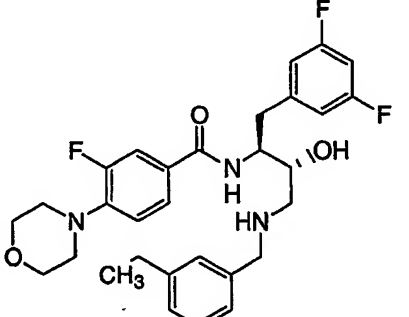
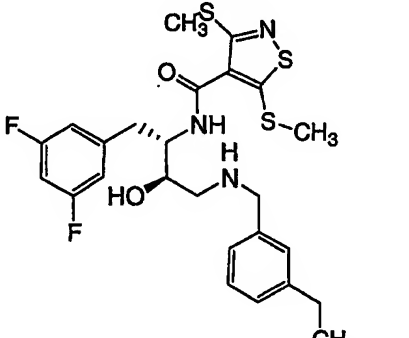
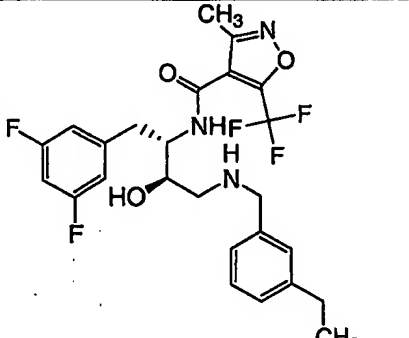
3720		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-3-furamide	
3721		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxy-6-neopentylpyridine-2-carboxamide	
3722		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,3-thiazole-4-carboxamide	
3723		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxy-7-methoxy-1-benzothiophene-5-carboxamide	
3724		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxy-7-methoxy-1-benzofuran-5-carboxamide	

3725		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenyl-1,3-oxazole-4-carboxamide	
3726		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,4-dihydroxybenzamide	
3727		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁴-phenylsuccinamide	
3728		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁴-pyridin-3-ylsuccinamide	

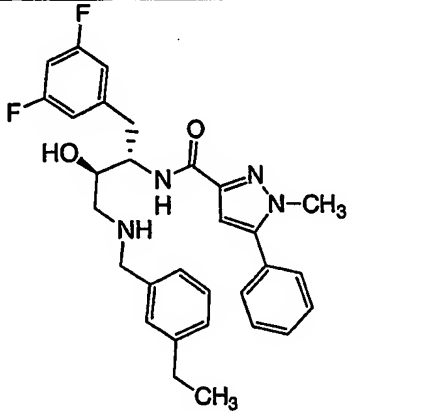
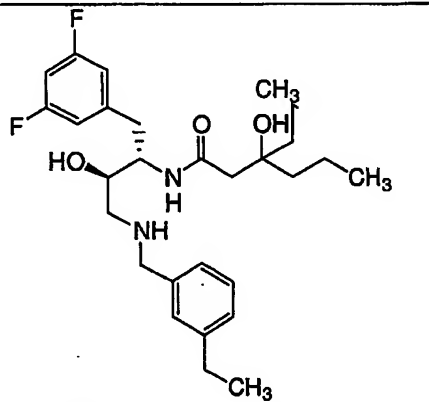
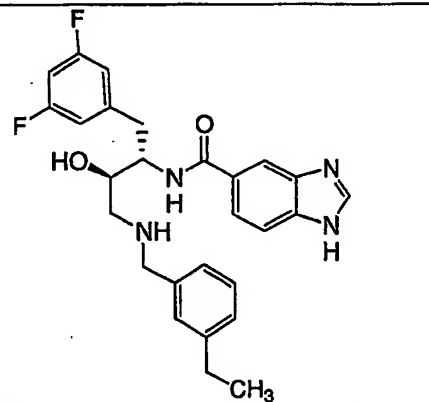
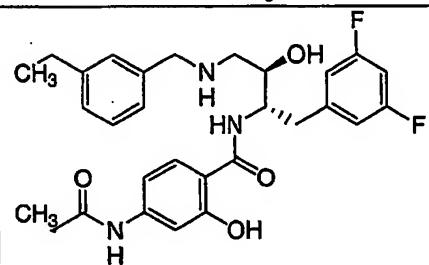
3729		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁴-(2,6-dimethylphenyl)succinamide	
3730		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N⁴-methylsuccinamide	
3731		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4-methoxyphenoxy)propanamide	
3732		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxy-7-methoxyquinoline-3-carboxamide	
3733		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[methyl(methylsulfonyl)amino]benzamide	

3734		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(pyrrolidin-3-ylsulfonyl)benzamide	572.2
3735		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxamide	
3736		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide	
3737		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3-thiazole-4-carboxamide	
3738		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenylimidazo[1,2-a]pyridine-6-carboxamide	

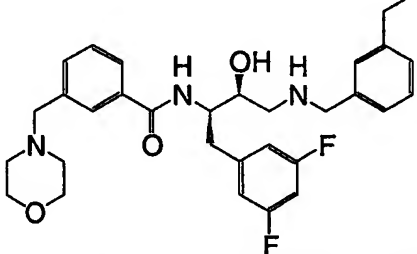
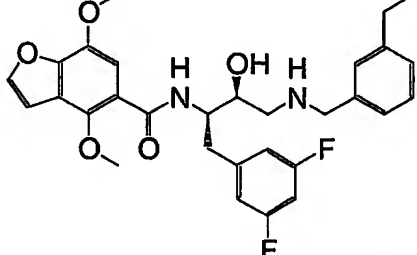
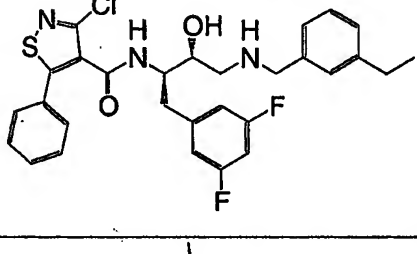
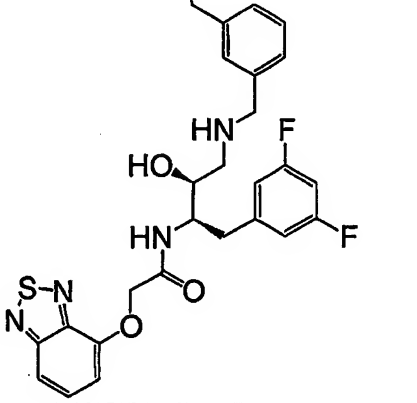
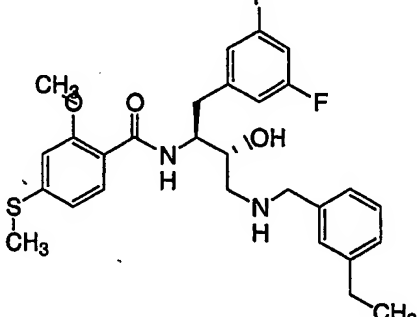
3739		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ⁵ -(1,3-thiazol-2-yl)pentanediamide	
3740		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(4-methyl-1,2,3-thiadiazol-5-yl)thio]acetamide	
3741		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(piperidin-1-ylmethyl)-2-furamide	
3742		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxamide	

3743		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide	
3744		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-fluoro-4-morpholin-4-ylbenzamide	
3745		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3,5-bis(methylthio)isothiazole-4-carboxamide	
3746		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-methyl-5-(trifluoromethyl)isoxazole-4-carboxamide	

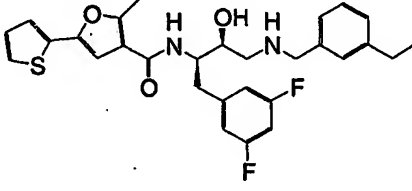
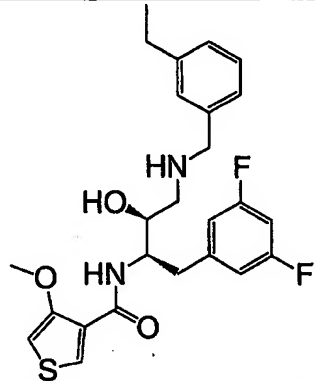
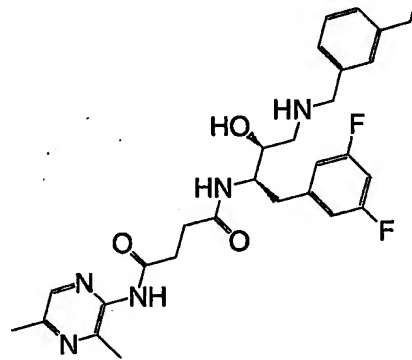
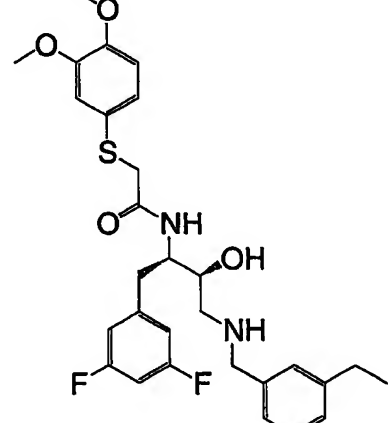
3747		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-5-(propionylamino)benzamide	
3748		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-phenyl-1H-pyrrole-2-carboxamide	
3749		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)pyrazine-2-carboxamide 4-oxide	
3750		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-1-pyridin-4-yl-1H-1,2,3-triazole-4-carboxamide	
3751		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methoxypyrazine-2-carboxamide 4-oxide	

3752		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-5-phenyl-1H-pyrazole-3-carboxamide	
3753		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxy-3-propylhexanamide	
3754		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-benzimidazole-5-carboxamide	
3755		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-(propionylamino)benzamide	

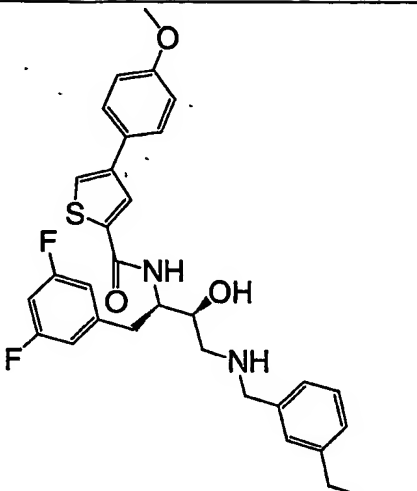
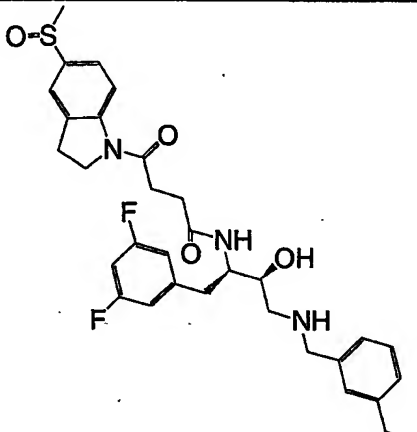
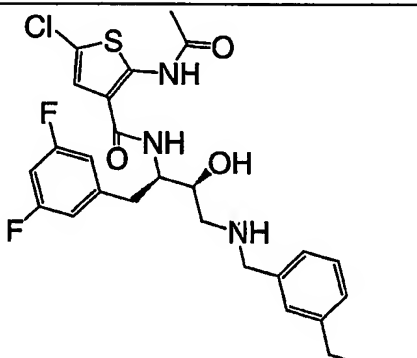
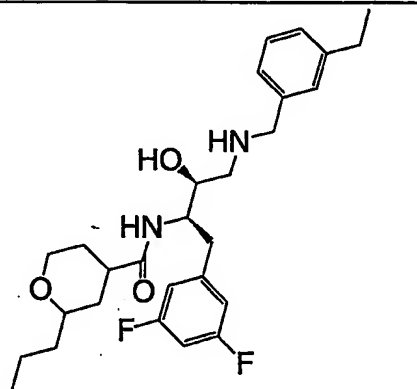
3756		5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1-benzofuran-2-carboxamide	
3757		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-pyridin-3-yl-1,3-thiazole-4-carboxamide	
3758		8-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-hydroxyquinoline-3-carboxamide	
3759		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1,6-naphthyridine-2-carboxamide	
3760		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2,2-dimethyl-4-oxochromane-6-carboxamide	

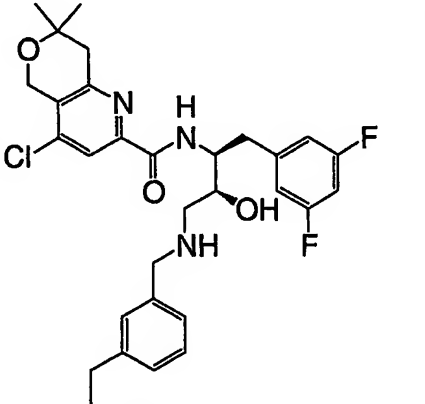
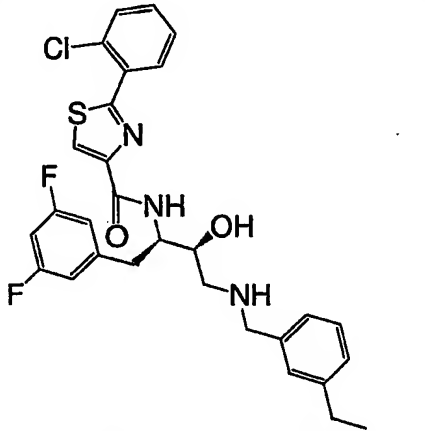
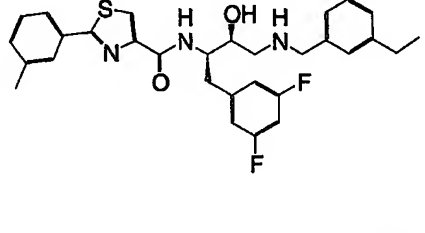
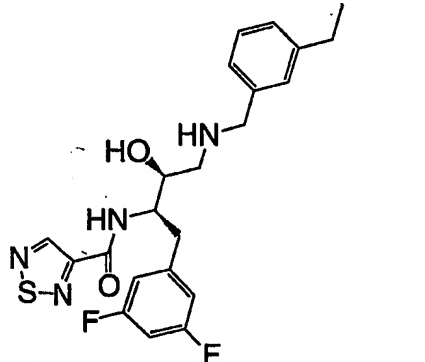
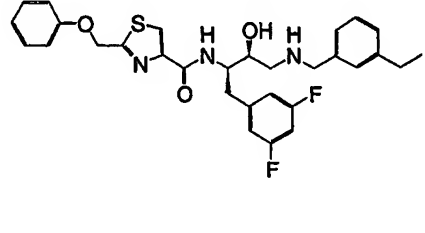
3761		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(morpholin-4-ylmethyl)benzamide	
3762		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,7-dimethoxy-1-benzofuran-5-carboxamide	
3763		3-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-phenylisothiazole-4-carboxamide	
3764		2-(2,1,3-benzothiadiazol-4-yl)oxy-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide	
3765		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methoxy-4-(methylthio)benzamide	

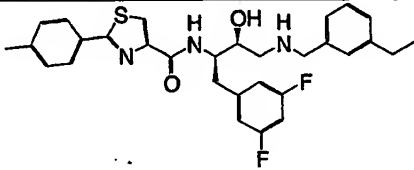
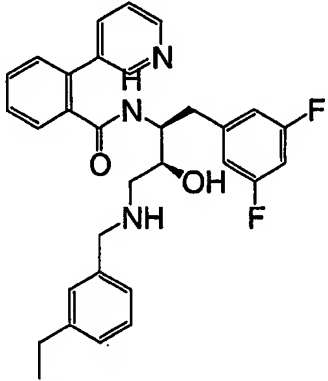
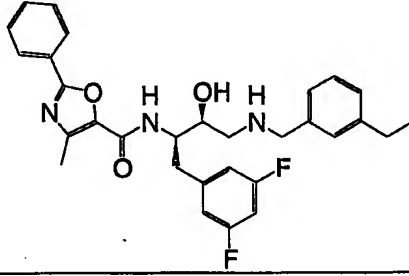
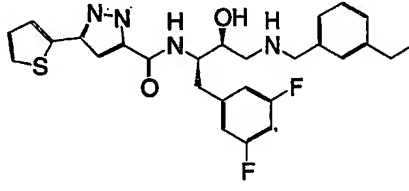
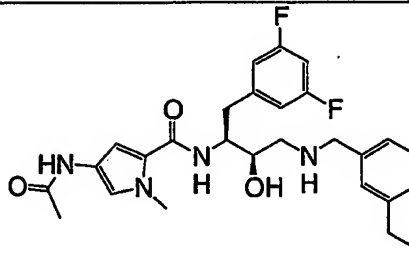
3766		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(4-methyl-1,3-thiazol-2-yl)thio]acetamide	
3767		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methoxy-1-benzofuran-2-carboxamide	
3768		5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-morpholin-4-ylbenzamide	
3769		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methoxy-1H-pyrrole-3-carboxamide	
3770		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-1,3-thiazole-4-carboxamide	

3771		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-5-(2-thienyl)-3-furamide	
3772		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methoxythiophene-3-carboxamide	
3773		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N'-(3,5-dimethylpyrazin-2-yl)succinamide	
3774		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(3,4-dimethoxyphenyl)thio]acetamide	

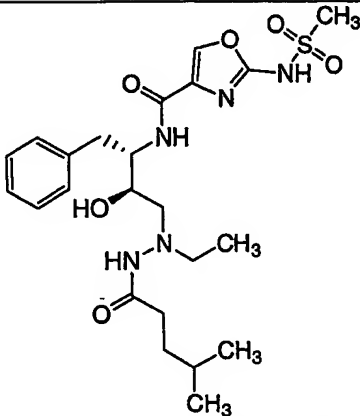
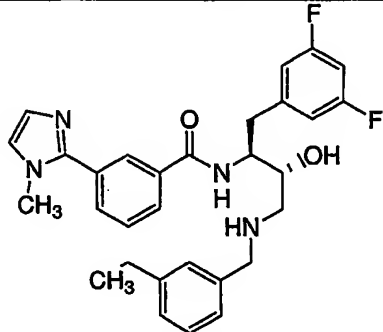
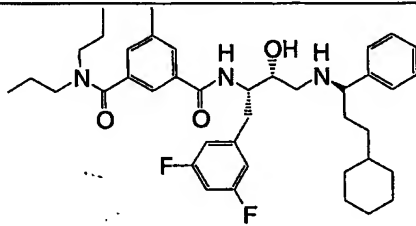
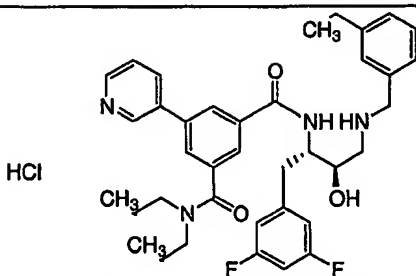
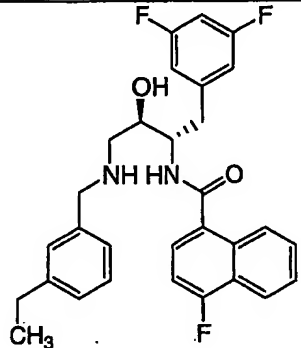
3775		N-(1-cyclopropylethyl)-N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-phenylsuccinamide
3776		6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(trifluoromethyl)pyridine-2-carboxamide
3777		N-(2-acetyl-3-thienyl)-N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succinamide
3778		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(4-fluorophenyl)-5-methyl-1H-1,2,4-triazole-3-carboxamide
3779		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N'-[2-fluoro-5-(methylsulfonyl)phenyl]succinamide

3780		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-methoxyphenyl)thiophene-2-carboxamide	
3781		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[5-(methylsulfinyl)-2,3-dihydro-1H-indol-1-yl]-4-oxobutanamide	
3782		2-(acetylamino)-5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thiophene-3-carboxamide	
3783		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-propyltetrahydro-2H-pyran-4-carboxamide	

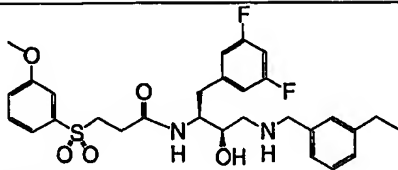
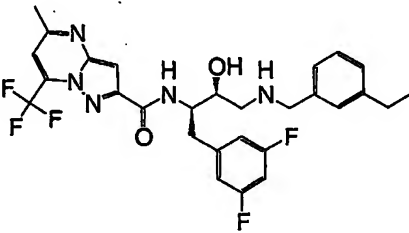
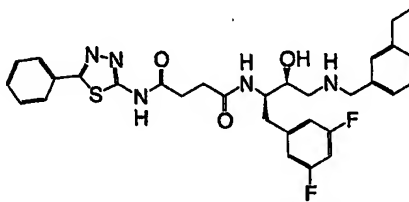
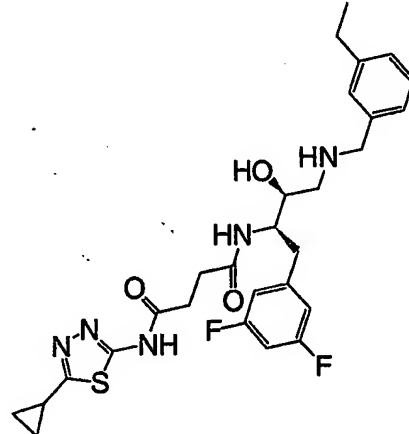
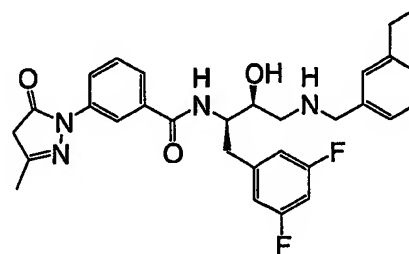
3784		4-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-2-carboxamide	
3785		2-(2-chlorophenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1,3-thiazole-4-carboxamide	
3786		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(3-methylphenyl)-1,3-thiazole-4-carboxamide	
3787		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-1,2,5-thiadiazole-3-carboxamide	
3788		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-(phenoxy)methyl-1,3-thiazole-4-carboxamide	

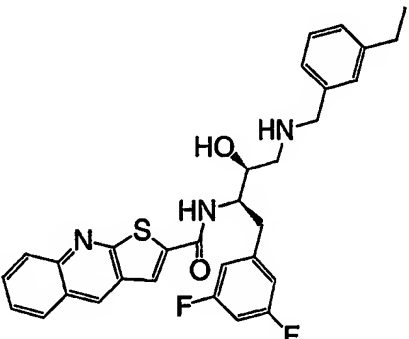
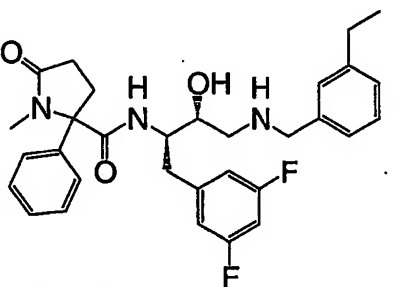
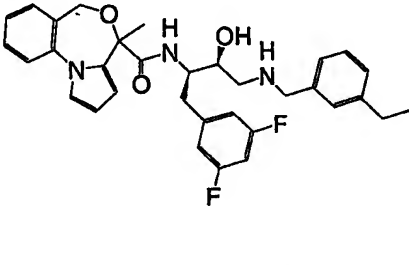
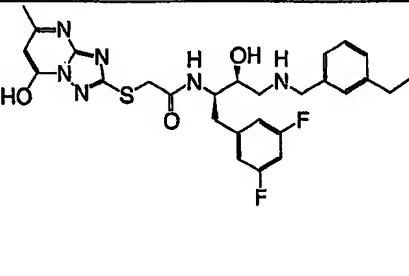
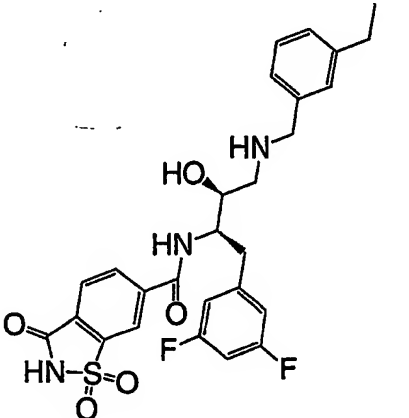
3789		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(4-methylphenyl)-1,3-thiazole-4-carboxamide	
3790		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-pyridin-3-ylbenzamide	
3791		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methyl-2-phenyl-1,3-oxazole-5-carboxamide	
3792		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-ethyl-3-(2-thienyl)-1H-pyrazole-5-carboxamide	
3793		4-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1H-pyrrole-2-carboxamide	

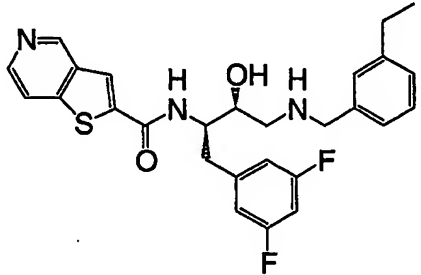
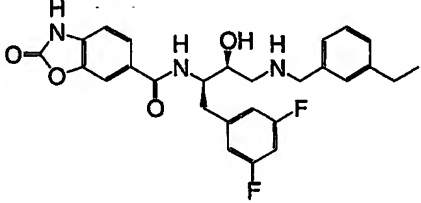
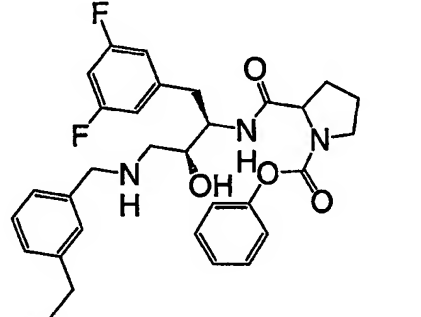
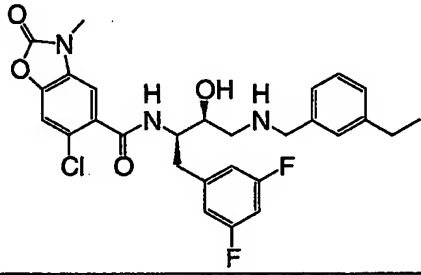
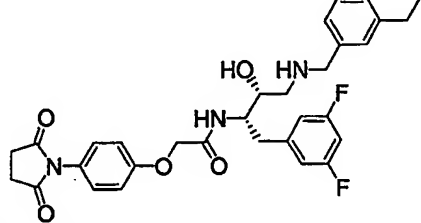
3794		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2,6-dimethylphenoxy)propanamide	
3795		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-phenyl-1,2,3-thiadiazole-5-carboxamide	
3796		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)thiophene-3-carboxamide	
3797		5-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxybenzamide	
3798		4-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)butanamide trifluoroacetate	

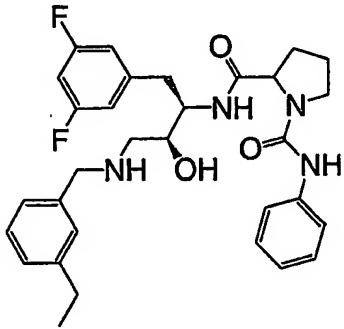
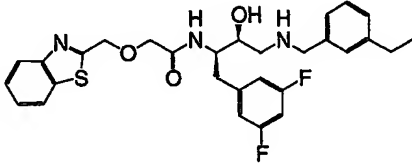
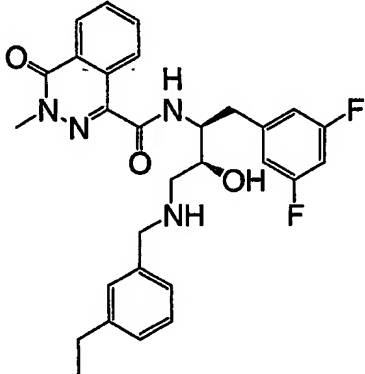
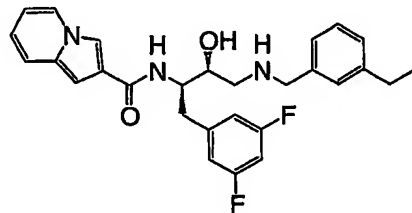
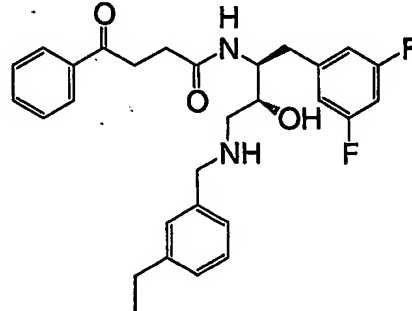
3799		N-((1S,2R)-1-benzyl-3-[1-ethyl-2-(4-methylpentanoyl)hydrazino]-2-hydroxypropyl)-2-[(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	
3800		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(1-methyl-1H-imidazol-2-yl)benzamide	519
3801		N'-[(1S,2R)-3-[(1R)-3-cyclohexyl-1-phenylpropyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3802		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N ³ ,N ³ -dipropyl-5-pyridin-3-ylisophthalamide hydrochloride	
3803		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-fluoro-1-naphthamide	

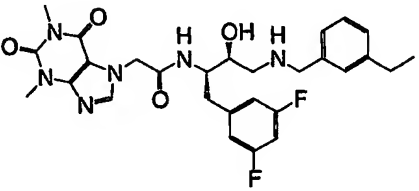
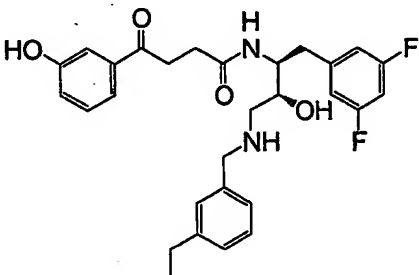
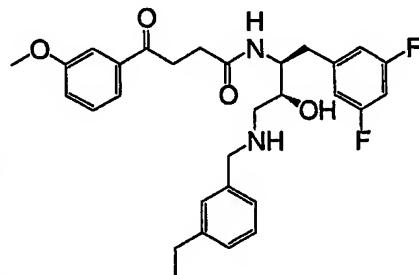
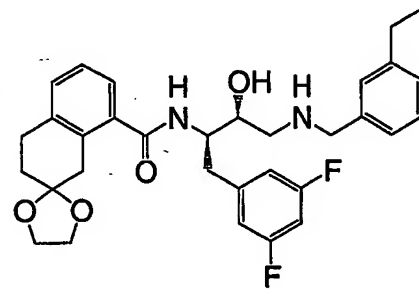
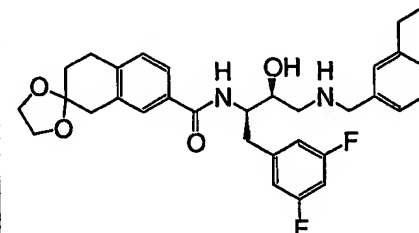
3804		N-cyclohexyl-N'- {(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N,5- dimethylisophthalamid e	
3805		N-[(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl]-1- methyl-1H-imidazole- 2-carboxamide	443.2
3806		N¹-[(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl]-N³- [oxo(phenyl)methyl]- L-alaninamide	
3807		N¹-[(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl]-N²- [imino(phenyl)methyl] glycinamide	
3808		N¹-[(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl]-N³-(2- propylpentanimidoyl)- L-alaninamide	
3809		6-(4-benzylpiperazin- 1-yl)-N-[(1S,2R)-1- (3,5-difluorobenzyl)- 2-hydroxy-3-[(3- iodobenzyl)amino]prop yl]nicotinamide	

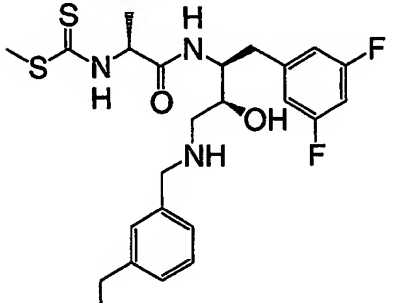
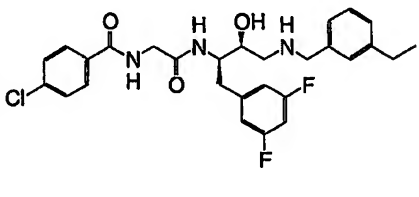
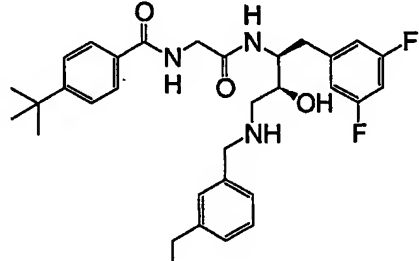
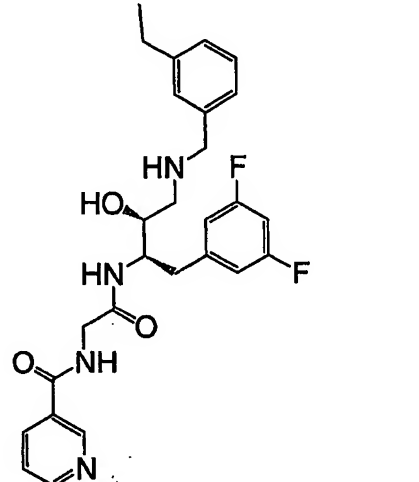
3810	 <p>as drawn</p>	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(3-methoxyphenyl)sulfonyl]propanamide	
3811		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide	
3812		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N'-(5-phenyl-1,3,4-thiadiazol-2-yl)succinamide	
3813		N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide	
3814		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	

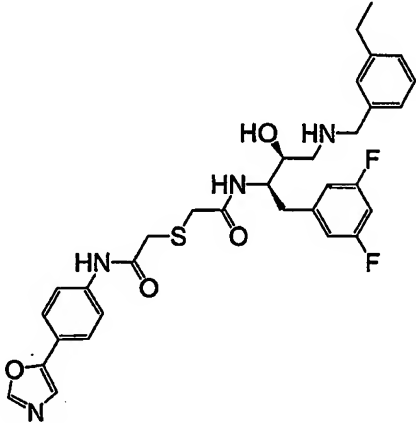
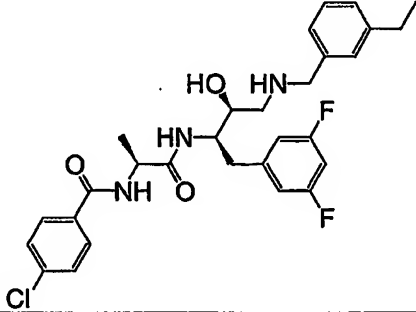
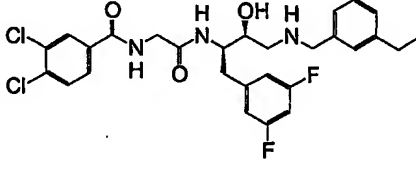
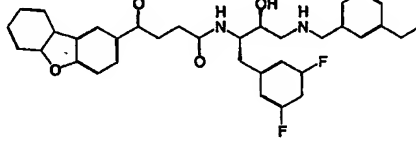
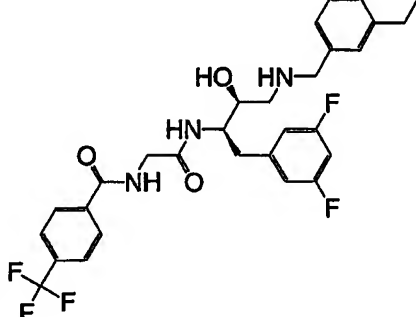
3815		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thieno[2,3-b]quinoline-2-carboxamide	
3816		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-5-oxo-2-phenylprolinamide	
3817		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine-4-carboxamide	
3818		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(7-hydroxy-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)thio]acetamide	
3819		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-oxo-2,3-dihydro-1,2-benzisothiazole-6-carboxamide 1,1-dioxide	

3820		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thieno[3,2-c]pyridine-2-carboxamide	
3821		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carboxamide	
3822		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-[oxo(phenoxy)methyl]p rolinamide	
3823		6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-5-carboxamide	
3824		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[4-(2,5-dioxopyrrolidin-1-yl)phenoxy]acetamide	

3825		N ² -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ¹ -phenylpyrrolidine-1,2-dicarboxamide	
3826		2-(1,3-benzothiazol-2-ylmethoxy)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide	
3827		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-4-oxo-3,4-dihydrophthalazine-1-carboxamide	
3828		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}indolizine-2-carboxamide	
3829		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxo-4-phenylbutanamide	

3830		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)acetamide	
3831		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3-hydroxyphenyl)-4-oxobutanamide	
3832		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3-methoxyphenyl)-4-oxobutanamide	
3833		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3',4'-dihydro-1'H-spiro[1,3-dioxolane-2,2'-naphthalene]-8'-carboxamide	
3834		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3',4'-dihydro-1'H-spiro[1,3-dioxolane-2,2'-naphthalene]-7'-carboxamide	

3835		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N²-[mercapto(methylthio)methyl]-D-alaninamide	
3836		N²-[(4-chlorophenyl)(oxo)methyl]-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]glycinamide	
3837		N²-[(4-tert-butylphenyl)(oxo)methyl]-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]glycinamide	
3838		N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N²-[oxo(pyridin-3-yl)methyl]glycinamide	

3839		2-[[2-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-2-oxoethyl]thio]-N-[4-(1,3-oxazol-5-yl)phenyl]acetamide	
3840		N ² -[(4-chlorophenyl)(oxo)methyl]-N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide	
3841		N ² -[(3,4-dichlorophenyl)(oxo)methyl]-N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}glycinamide	
3842		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5a,9a-dihydrodibenzo[b,d]furan-2-yl)-4-oxobutanamide	
3843		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ² -{oxo[4-(trifluoromethyl)phenyl]methyl}glycinamide	

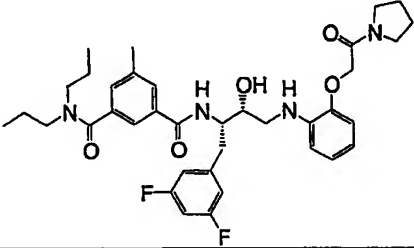
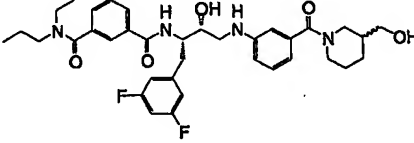
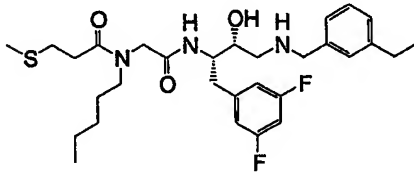
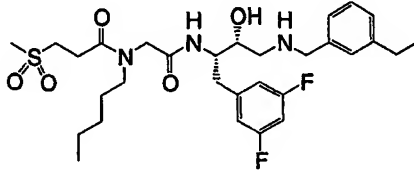
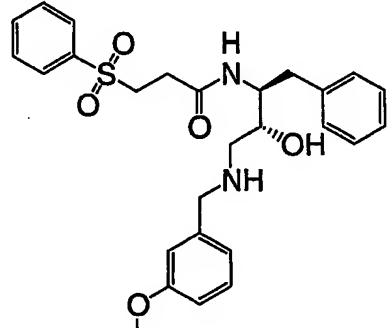
3844		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[(2,6-difluorophenyl)(oxo)methyl]glycinamide	
3845		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[oxo(4-methoxyphenyl)methyl]glycinamide	
3846		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-oxo-1,3-oxazolidin-3-yl)benzamide	
3847		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(phenylethynyl)nicotinamide	
3848		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N³-[oxo(1H-1,2,4-triazol-5-yl)methyl]-D-alaninamide	
3849		2-[[2-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino]-2-oxoethyl]thio-N-(pyridin-4-ylmethyl)acetamide	

3850		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(methoxymethyl)thio]benzamide	
3851		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4-oxobutanamide	
3852		4-(4-benzyl-1,4-diazepan-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxobutanamide	
3853		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,5-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxamide	
3854		N-[(dimethylamino)sulfonyl]glycyl-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)glycinamide	

3855		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxy-1-[(1R,2R)-2-hydroxycyclohexyl]prolinamide	
3856		(2S,3S)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide	
3857		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide	
3858		N-(2-cyano-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide	
3859		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2,5-dioxoimidazolidin-4-yl)acetamide	

3860		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)acetamide	
3861		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(2-furymethyl)-5-oxopyrrolidine-3-carboxamide	
3862		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxo-4-(5-oxo-1,4-diazepan-1-yl)butanamide	
3863		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4-methylphenyl)-4,5-dihydro-1H-pyrazole-5-carboxamide	
3864		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,1,3-benzoxadiazole-5-carboxamide 1-oxide	

3865		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-pyridin-3-ylpiperidin-1-yl)propanamide	
3866		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxo-4-(2-propyl-1H-imidazol-1-yl)butanamide	
3867		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4a,9a-dihydro-9H-carbazole-9-carboxamide	
3868		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methyl-4-oxo-1-phenyl-1,4-dihydropyridazine-3-carboxamide	
3869		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-methyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrrol-3-yl]amino)propyl)-5-methyl-N,N-dipropylisophthalamide	

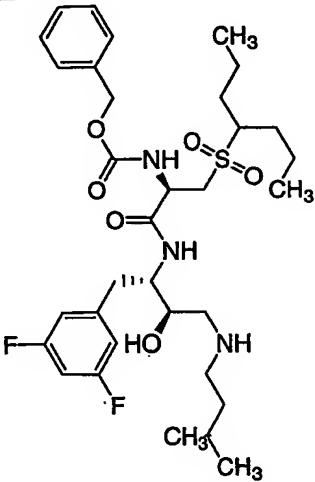
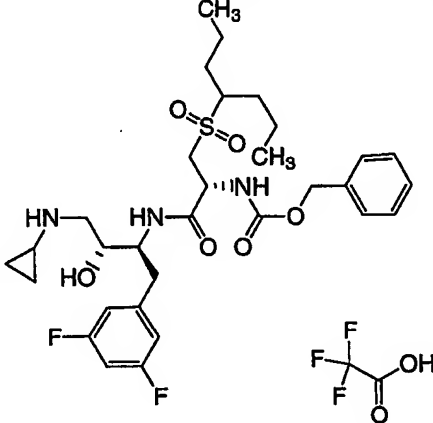
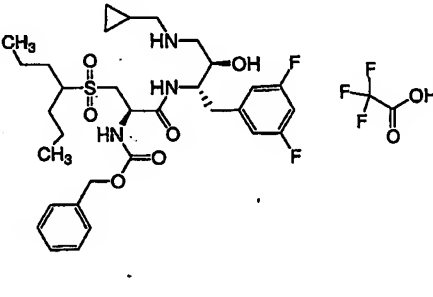
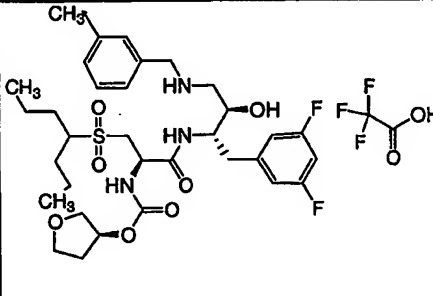
3870		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([2-(2-oxo-2-pyrrolidin-1-ylethoxy)phenyl]amino)propyl)-5-methyl-N,N-dipropylisophthalamide
3871		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-([3-(hydroxymethyl)piperidin-1-yl]carbonyl)phenyl]amino)propyl)-5-methyl-N,N-dipropylisophthalamide
3872		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(ethylbenzyl)amino]-2-hydroxypropyl)-N^2-[3-(methylthio)-1-oxopropyl]-N^2-pentylglycinamide
3873		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-(ethylbenzyl)amino]-2-hydroxypropyl)-N^2-[3-(methylsulfonyl)-1-oxopropyl]-N^2-pentylglycinamide
3874		N-((1S,2R)-1-benzyl-2-hydroxy-3-([3-methoxybenzyl]amino)propyl)-3-(phenylsulfonyl)propanamide

3875		N'-(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-oxabicyclo[2.2.1]hept-2-ylmethyl)amino]propyl)-5-methyl-N,N-dipropylisophthalamide	
3876		N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3R)-2-oxo-1-propylazepan-3-yl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide	
3877		N'-[(1S,2R)-3-[(1-acetylpiperidin-4-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3878		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-[2-(dimethylamino)-2-oxoethyl]-N,5-dimethylisophthalamide	
3879		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-[2-(dimethylamino)ethyl]-N-ethyl-5-methylisophthalamide	
3880		N-benzyl-N'-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N,5-dimethylisophthalamide	

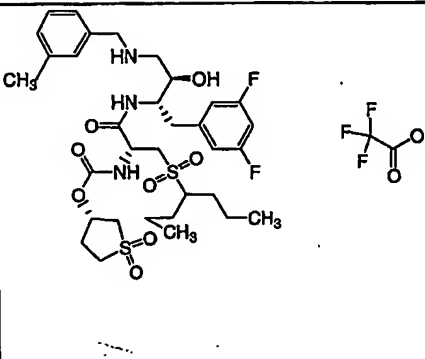
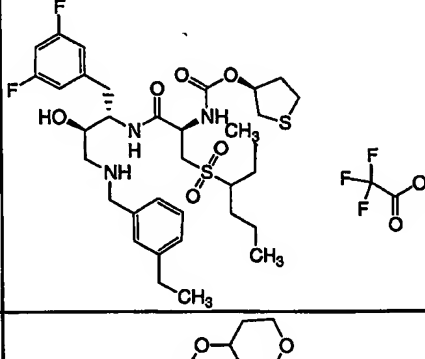
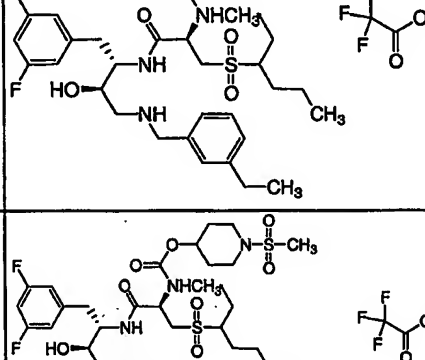
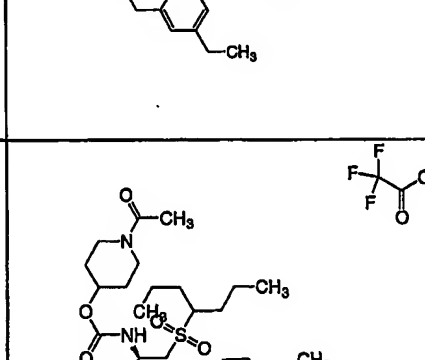
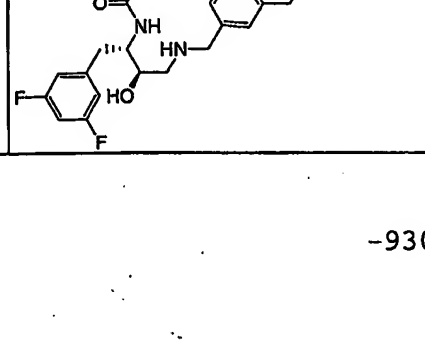
3881		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-{[2-(2-hydroxyethyl)piperidin-1-yl]carbonyl}-5-methylbenzamide	
3882		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N,5-dimethyl-N-(2-phenylethyl)isophthalamide	
3883		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(3-formyl-2-furyl)benzyl]amino}-2-hydroxypropyl)-5-methyl-N,N-dipropylisophthalamide	
3884		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(5-formyl-2-thienyl)benzyl]amino}-2-hydroxypropyl)-5-methyl-N,N-dipropylisophthalamide	
3885		N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N,5-dimethyl-N-(2-pyridin-2-ylethyl)isophthalamide	
3886		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({[1-(methylsulfonyl)piperidin-4-yl]methyl}amino)propyl]-5-methyl-N,N-dipropylisophthalamide	

3887		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N ³ ,N ³ -diethylpiperidine-1,3-dicarboxamide	
3888		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N ³ ,N ³ -dipropylpiperidine-1,3-dicarboxamide	
3889		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[3-(5-formyl-4-methyl-2-thienyl)benzyl]amino]-2-hydroxypropyl}-5-methyl-N,N-dipropylisophthalamide	
3890		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(1-phenylvinyl)benzyl]amino]propyl}-5-methyl-N,N-dipropylisophthalamide	
3891		N'-[(1S,2R)-3-[(3-bicyclo[2.2.1]hept-2-ylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3892		ethyl 3-[3-(((2R,3S)-4-(3,5-difluorophenyl)-3-((3-((dipropylamino)carbonyl)-5-methylbenzoyl)amino)-2-hydroxybutyl]amino)methyl)phenyl]propanoate	

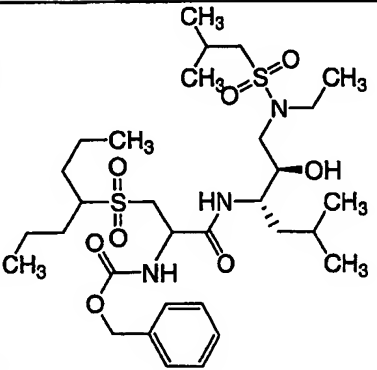
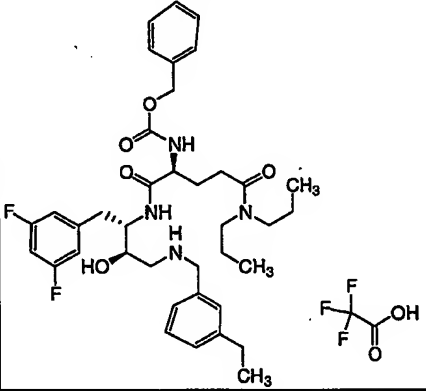
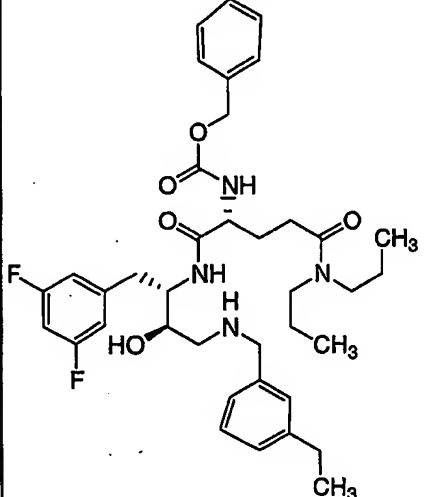
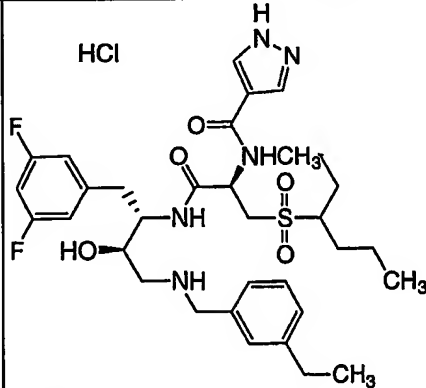
3893		ethyl 4-[3- (((2R,3S)-4-(3,5- difluorophenyl)-3- (3- [(dipropylamino)carbo nyl]-5- methylbenzoyl)amino)- 2- hydroxybutyl)amino]me thyl)phenyl]butanoate	
3894		methyl (2R)-3-[3- (((2R,3S)-4-(3,5- difluorophenyl)-3-((3- [(dipropylamino)carbon yl]-5- methylbenzoyl)amino)- 2- hydroxybutyl)amino)met hyl)phenyl]-2- methylpropanoate	
3895		ethyl 3'-(((2R,3S)-4- (3,5-difluorophenyl)- 3-((3- [(dipropylamino)carbon yl]-5- methylbenzoyl)amino)- 2- hydroxybutyl)amino)met hyl)biphenyl-2- carboxylate	
3896		2-{1-[2-(((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)amino)- 2- oxoethyl]cyclopentyl}- N,N-dipropylacetamide	
3897		N ² - [(benzyloxy)carbonyl]- N ¹ -((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide trifluoroacetate	702

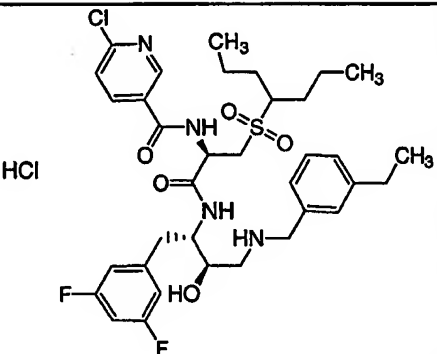
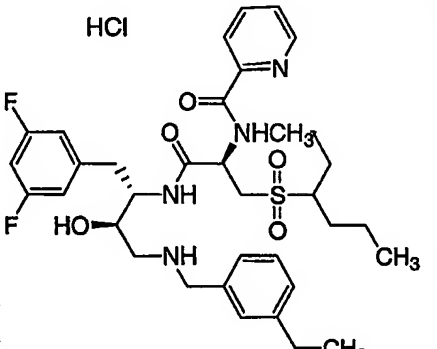
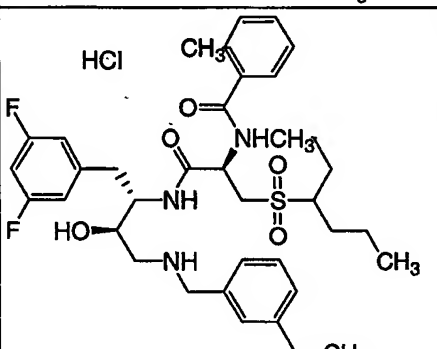
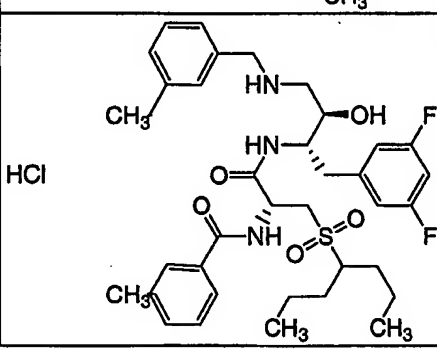
3898		N^2 - [(benzyloxy) carbonyl]- N^1 -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- methylbutyl) amino]-2- hydroxypropyl}-3-[(1- propylbutyl) sulfonyl]- D,L-alaninamide	654
3899		N^2 - [(benzyloxy) carbonyl]- N^1 -{(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-3-[(1- propylbutyl) sulfonyl]- D,L-alaninamide trifluoroacetate	624
3900		N^2 - [(benzyloxy) carbonyl]- N^1 -{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(cyclopropylmethyl) am- ino]-2-hydroxypropyl}- 3-[(1- propylbutyl) sulfonyl]- D,L-alaninamide trifluoroacetate	638
3901		N^1 -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}- N^2 - {[(3S)- tetrahydrofuran-3- yloxy] carbonyl}-3-[(1- propylbutyl) sulfonyl]- L-alaninamide trifluoroacetate	682

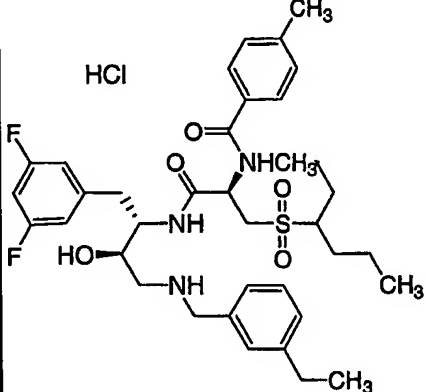
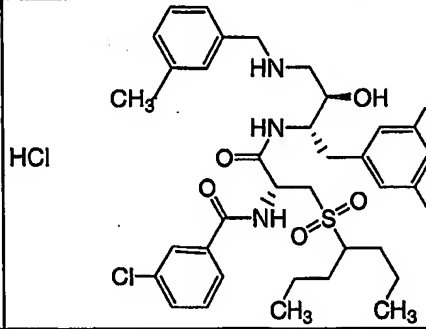
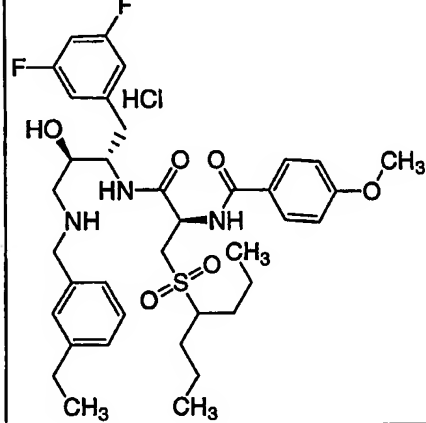
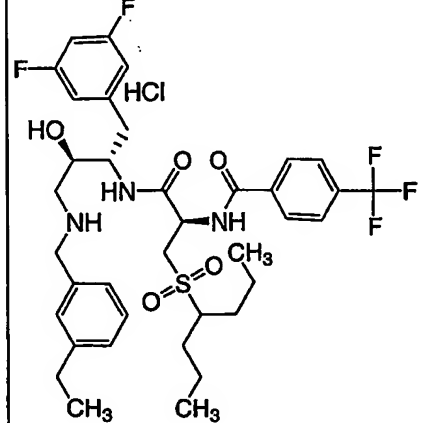
3902		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-(((3S)-tetrahydrofuran-3-yloxy)carbonyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate	682
3903		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-(((3S)-tetrahydrofuran-3-yloxy)carbonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	682
3904		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-(((3R)-tetrahydrofuran-3-yloxy)carbonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	682
3905		N¹-((1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-N²-(((3S)-tetrahydrofuran-3-yloxy)carbonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	648

3906		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^2 -{[(3S)-1,1-dioxidotetrahydrothien-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	730
3907		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^2 -{[(3S)-tetrahydrothiophen-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	698
3908		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^2 -{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	696
3909		N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^2 -{[1-(methylsulfonyl)piperidin-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	773
3910		N^2 -{[1-acetylpiperidin-4-yloxy]carbonyl}- N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	737

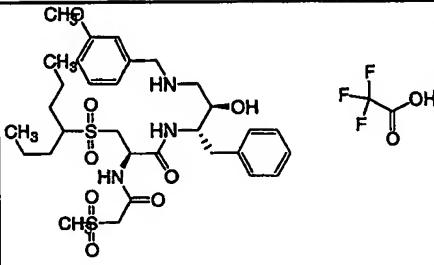
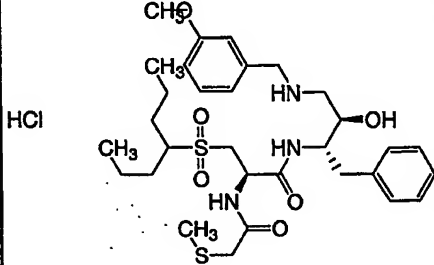
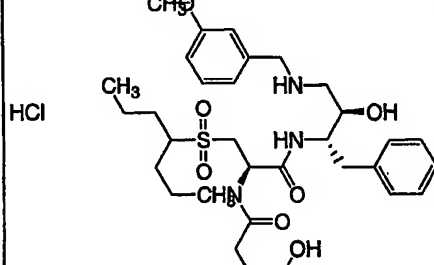
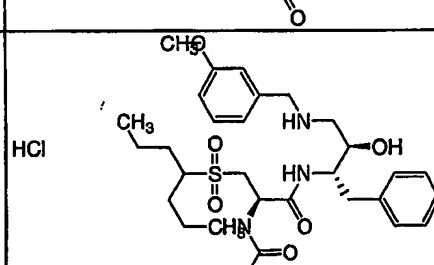
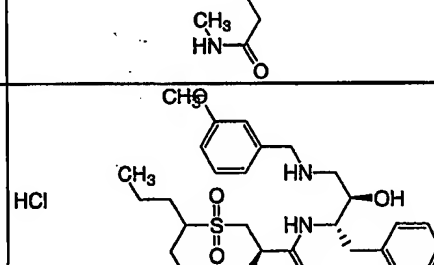
3911		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[[[(3R)-5-oxopyrrolidin-3-yl)methyl]carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	709
3912		N¹-((1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-N²-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	668
3913		N²-[(benzyloxy)carbonyl]-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl)ethyl]amino]propyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	718
3914		N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[[[(3S)-tetrahydrofuran-3-yloxy]carbonyl]-D-leucinamide trifluoroacetate	562
3915		N¹-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-[(benzyloxy)carbonyl]-L-leucinamide hydrochloride	548

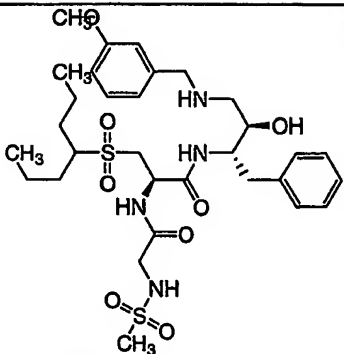
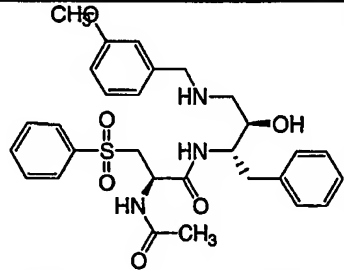
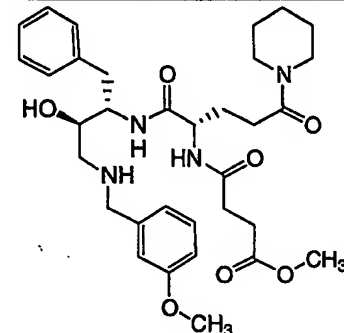
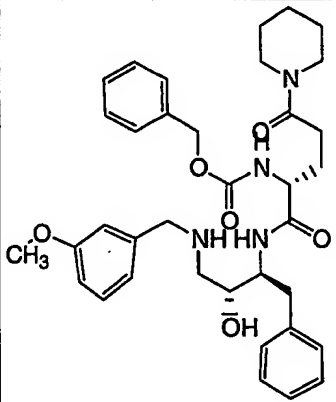
3916		N ² -[(benzyloxy) carbonyl]-N ¹ -((1S)-1-((1R)-2-ethyl(isobutylsulfonyl)amino)-1-hydroxyethyl)-3-methylbutyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide	662
3917		N ² -[(benzyloxy) carbonyl]-N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N ⁵ ,N ⁵ -dipropyl-L-glutamamide trifluoroacetate	681
3918		N ² -[(benzyloxy) carbonyl]-N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N ⁵ ,N ⁵ -dipropyl-D-glutamamide	681
3919		N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N ² -[(1H-pyrazol-4-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide hydrochloride	662

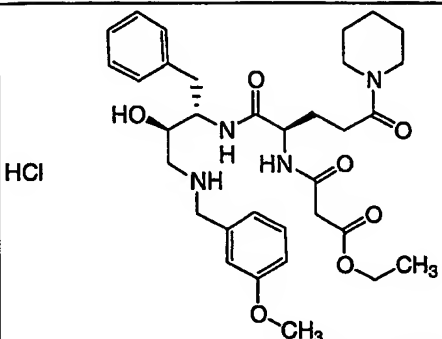
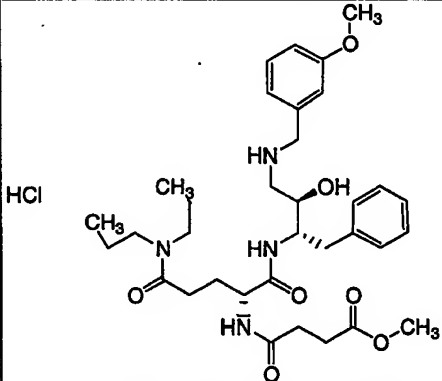
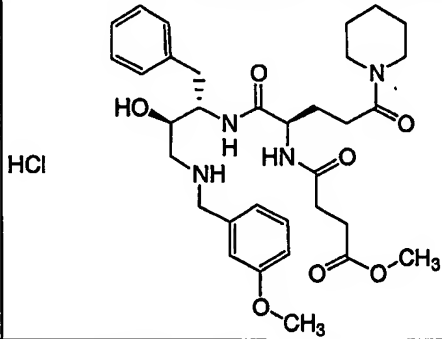
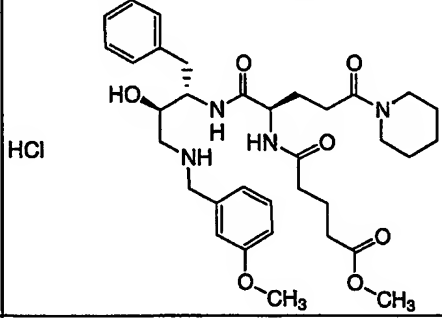
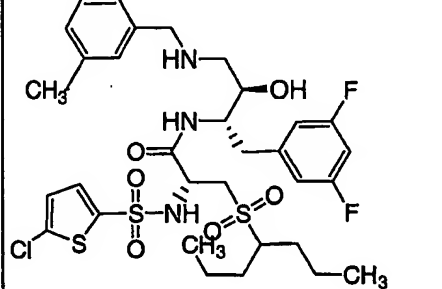
3920	 <p>HCl</p>	N^2 -[(6-chloropyridin-3-yl)carbonyl]- N^1 -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	707
3921	 <p>HCl</p>	N^1 -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]- N^2 -[(pyridin-2-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	673
3922	 <p>HCl</p>	N^1 -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]- N^2 -(2-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686
3923	 <p>HCl</p>	N^1 -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]- N^2 -(3-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686

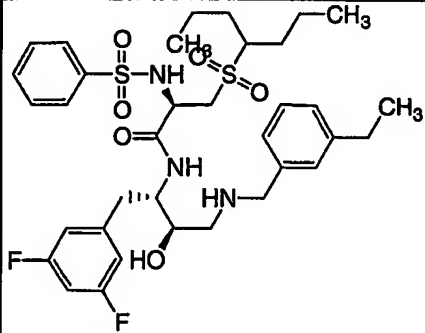
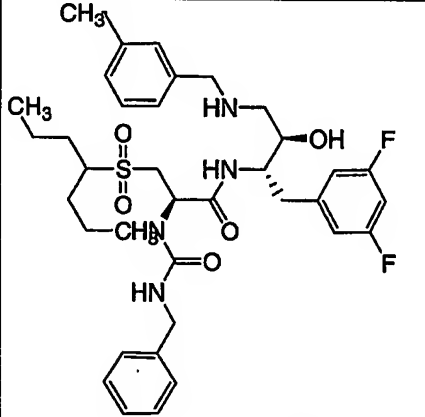
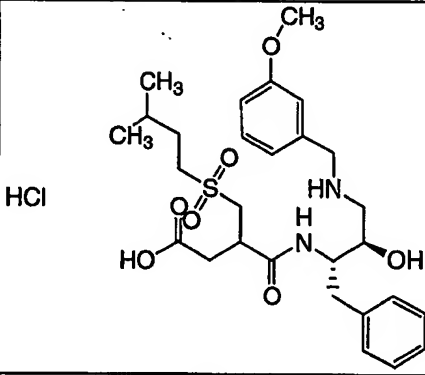
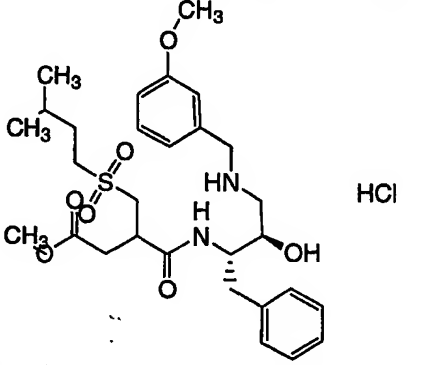
3924		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ² -(4-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686
3925		N ² -(3-chlorobenzoyl)-N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	706
3926		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ² -(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	702
3927		N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N ² -(4-trifluoromethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	740

3928	HCl 	N ² - (cyclohexylcarbonyl)- N ¹ -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide hydrochloride	678
3929		N ² (benzoyl)-N ¹ - {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide	672
3930		N ¹ -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N ² - (phenylacetyl)-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide	686
3931		N ¹ -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N ² -(3- phenylpropanoyl)-3- [(1- propylbutyl)sulfonyl]- D,L-alaninamide trifluoroacetate	700
3932	HCl 	N ¹ -{(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]pr opyl}-N ² - (cyclopropylacetyl)-3- [(1- propylbutyl)sulfonyl]- D,L-alaninamide hydrochloride	616

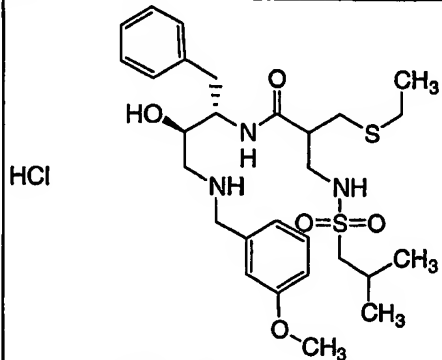
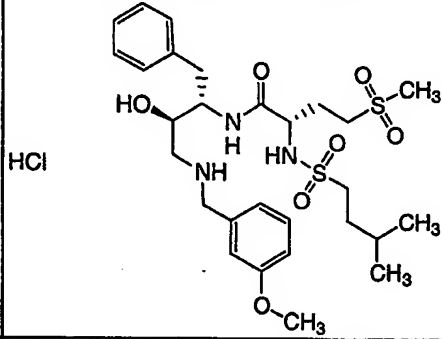
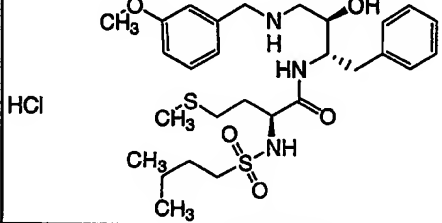
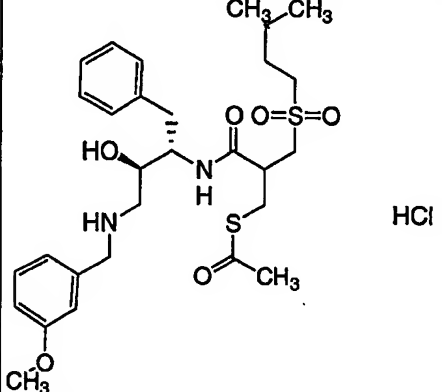
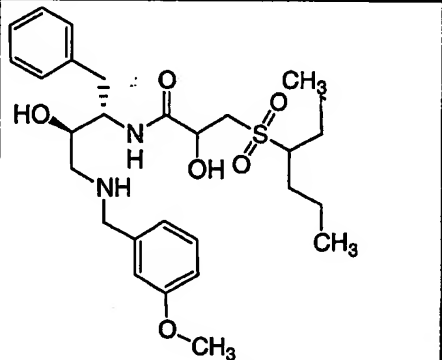
3933		N¹-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-[(methylsulfonyl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	654
3934		N¹-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-[(methylthio)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	622
3935		N¹-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-(4-hydroxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	634
3936		N¹-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-[4-(methylamino)-4-oxobutanoyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	647
3937		N¹-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-(4-methoxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	648

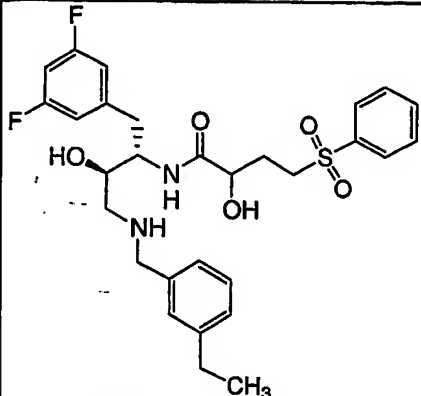
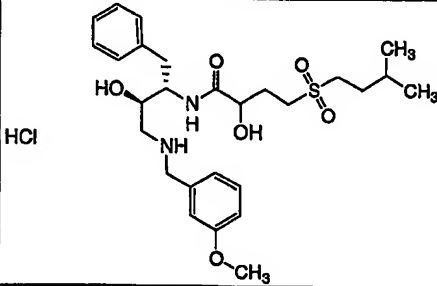
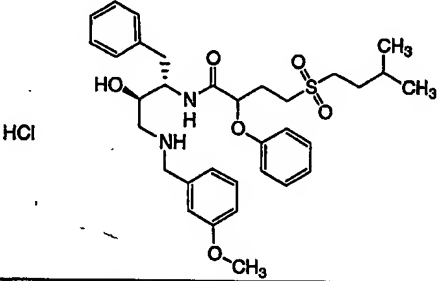
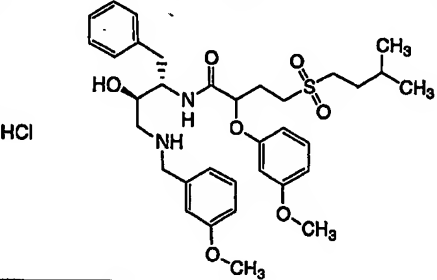
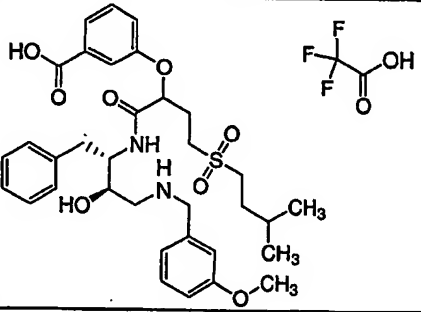
3938	HCl		N-(methanesulfonyl)glycyl-N¹-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride	669
3939	HCl		N²-acetyl-N¹-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-3-(phenylsulfonyl)-D,L-alaninamide hydrochloride	554
3940	HCl		(2S)-2-(4-methoxy-4-oxobutanoyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	611
3941	HCl		(2R)-2-(((benzyloxy)carbonyl)amino)-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	631

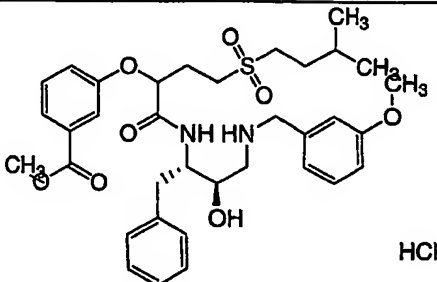
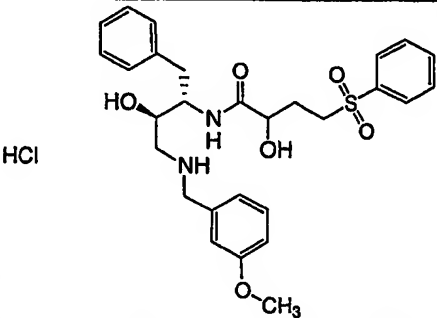
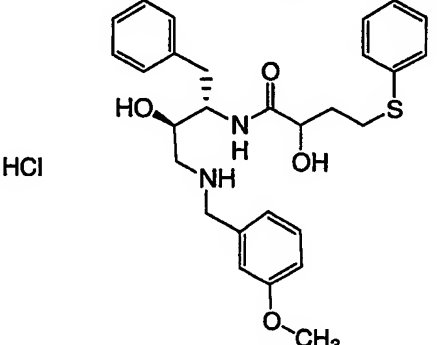
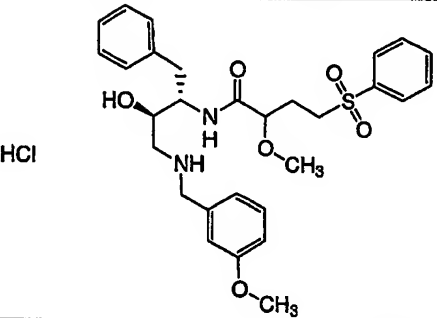
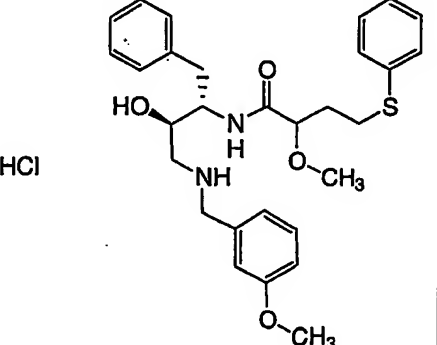
3942	 <p>HCl</p>	(2R)-2-(3-ethoxy-3-oxopropanoyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	611
3943	 <p>HCl</p>	N¹-((1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-N²-(4-methoxy-4-oxobutanoyl)-N⁵,N⁵-dipropyl-D-glutamamide hydrochloride	627
3944	 <p>HCl</p>	(2R)-2-(4-methoxy-4-oxobutanoyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	611
3945	 <p>HCl</p>	(2R)-2-(5-methoxy-5-oxopentanoyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	625
3946		N²-[(5-chlorothiophen-2-yl)sulfonyl]-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	748

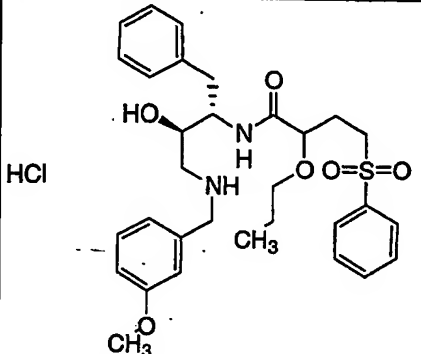
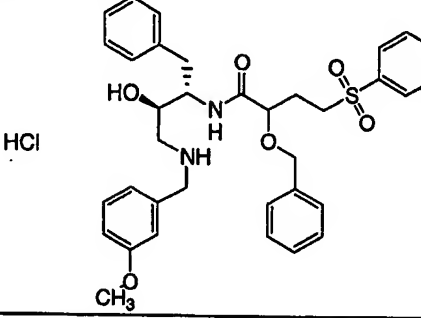
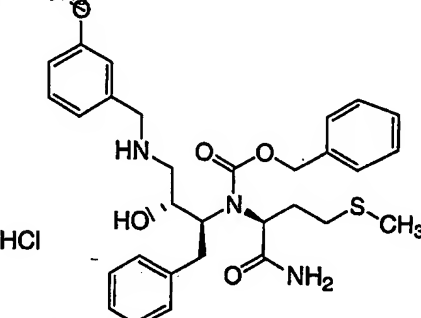
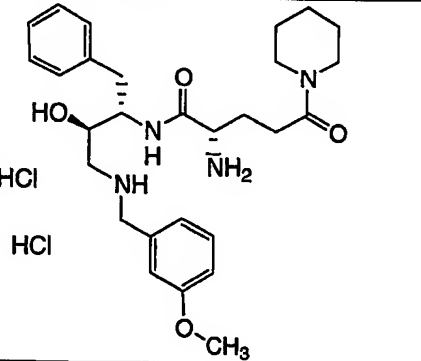
3947		N^1 -{(1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- N^2 -(phenylsulfonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	708
3948		N^2 -[(benzylamino)carbonyl]- N^1 -{(1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	701
3949		4-((1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoic acid hydrochloride	549
3950		methyl 4-((1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoate hydrochloride	563

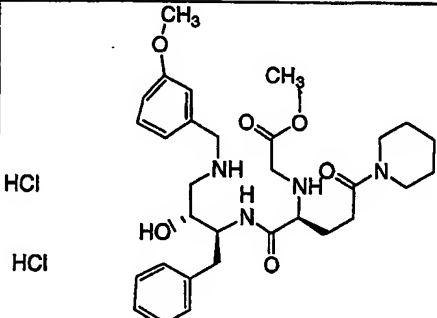
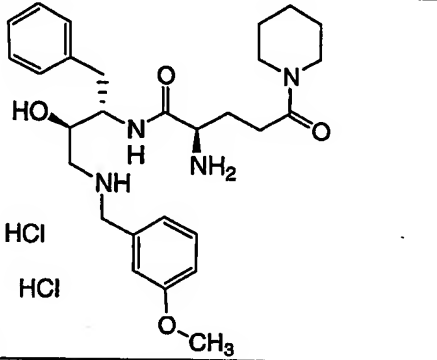
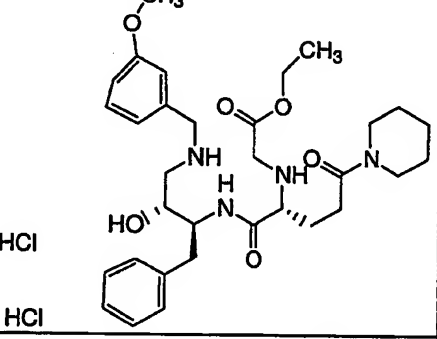
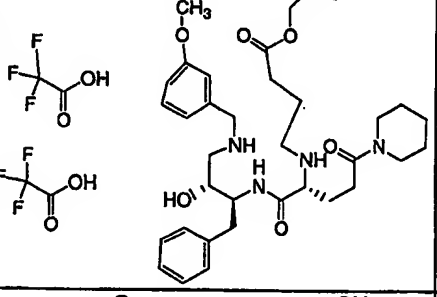
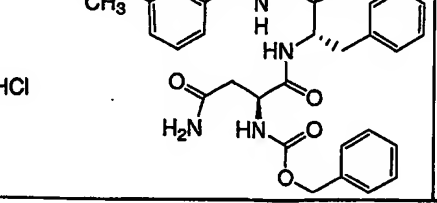
3951	HCl		N ¹ -{ (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]succinamide hydrochloride	548
3952	HCl		N ¹ -{ (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]-N ⁴ -methylsuccinamide hydrochloride	562
3953	HCl		N ¹ -{ (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]-N ⁴ ,N ⁴ -dimethylsuccinamide hydrochloride	576
3954			N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[(1-propylbutyl)sulfonyl]methylpropanamide	693
3955	HCl		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(ethylsulfonyl)-2-[(isobutylsulfonyl)amino]methylpropanamide hydrochloride	598

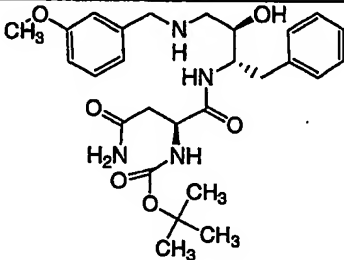
3956	 <p>HCl</p>	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-3-(ethylthio)-2-((isobutylsulfonyl)amino)methylpropanamide hydrochloride	566
3957	 <p>HCl</p>	(2S)-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-((isopentylsulfonyl)amino)-4-(methylsulfonyl)butanamide hydrochloride	598
3958	 <p>HCl</p>	N¹-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N²-(isopentylsulfonyl)-L-methioninamide hydrochloride	566
3959	 <p>HCl</p>	S-(3-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)amino)-2-((isopentylsulfonyl)methyl)-3-oxopropyl ethanethioate hydrochloride	579
3960		N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-hydroxy-3-((1-propylbutyl)sulfonyl)propanamide	535

3961		N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-(phenylsulfonyl)butanamide	561
3962		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-4-(isopentylsulfonyl)butanamide hydrochloride	521
3963		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4-(isopentylsulfonyl)-2-phenoxybutanamide hydrochloride	597
3964		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4-(isopentylsulfonyl)-2-(3-methoxyphenoxy)butanamide hydrochloride	627
3965		3-[1-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino]carbonyl]-3-(isopentylsulfonyl)propoxy]benzoic acid trifluoroacetate	641

3966	 <p>HCl</p>	<p>methyl 3-[1- [((1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl)amino)carbonyl] -3- (isopentylsulfonyl)pr opoxy]benzoate hydrochloride</p>	655
3967	 <p>HCl</p>	<p>N-((1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl)-2-hydroxy-4- (phenylsulfonyl)butan amide hydrochloride</p>	527
3968	 <p>HCl</p>	<p>N-((1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl)-2-hydroxy-4- (phenylthio)butanamid e hydrochloride</p>	495
3969	 <p>HCl</p>	<p>N-((1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl)-2-methoxy-4- (phenylsulfonyl)butan amide hydrochloride</p>	541
3970	 <p>HCl</p>	<p>N-((1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl)-2-methoxy-4- (phenylthio)butanamid e hydrochloride</p>	509

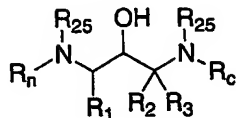
3971		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4-(phenylsulfonyl)-2-propoxybutanamide hydrochloride	569
3972		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-(benzyloxy)-4-(phenylsulfonyl)butanamide hydrochloride	617
3973		N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N²-[(benzyloxy)carbonyl]-D,L-methioninamide hydrochloride	566
3974		(2S)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	497

3975	 <p>HCl HCl</p>	(2S)-2-(2-ethoxy-2-oxoethyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	569
3976	 <p>HCl HCl</p>	(2R)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	497
3977	 <p>HCl HCl</p>	(2R)-2-(2-ethoxy-2-oxoethyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride	583
3978	 <p>CF₃COOH CF₃COOH</p>	(2R)-2-(4-ethoxy-4-oxobutanyl)amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide ditrifluoroacetate	611
3979	 <p>HCl</p>	N¹-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-N²-((benzyloxy)carbonyl)-L-aspartamide hydrochloride	549

3980	<p>HCl</p> 	<p>N¹-{(1<i>S</i>,2<i>R</i>)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N²-[(tertbutyloxy)carbonyl]-L-aspartamide hydrochloride</p>	515
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What is claimed is:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof wherein

- 5 where R_1 is:

(I) C_1 - C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1 - C_3 alkyl, C_3 - C_8 cycloalkyl (optionally substituted with C_1 - C_3 alkyl C_1 - C_3 alkoxy), -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C_1 - C_3 alkoxy, -NR_{1-a}R_{1-b}, and -OC=O-NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are independently at each occurrence -H or C_1 - C_6 alkyl,

(II) -CH₂-S(O)₀₋₂-(C_1 - C_6 alkyl),

(III) -CH₂-CH₂-S(O)₀₋₂-(C_1 - C_6 alkyl),

(IV) C_2 - C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C_1 - C_3 alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C_1 - C_6 alkyl,

(V) C_2 - C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C_1 - C_3 alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C_1 - C_6 alkyl,

(VI) -(CH₂)_{n1}-(R_{1-aryl}) where n_1 is zero or one and where R_{1-aryl} is phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl, or tetralinyl each of which is optionally substituted with one, two, three, four, or five of the following substituents on the aryl ring:

(A) C_1 - C_6 alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR_{1-a}R_{1-b}, -C≡N, -CF₃, and C_1 - C_3 alkoxy,

(B) C₂-C₆ alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(C) C₂-C₆ optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(D) -F, Cl, -Br and -I,

(E) -C₁-C₆ haloalkoxy

(F) -C₁-C₆ alkoxy

10 (G) -NR_{N-2}R_{N-3},

(H) -OH,

(I) -C≡N,

(J) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(K) -CO-(C₁-C₄ alkyl),

(L) -SO₂-NR_{1-a}R_{1-b},

(M) -CO-NR_{1-a}R_{1-b},

20 (N) -SO₂-(C₁-C₄ alkyl),

(VII) -(CH₂)_{n1}-(R_{1-heteroaryl}) where R_{1-heteroaryl} is selected from the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indoliziny, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuran, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuran, benzotetrahydrothienyl, purinyl,

benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl,
 pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl,
 dihydrobenzisoaxazinyl, benzisoaxazinyl, benzoxazinyl,
 dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl,
 5 coumarinyl, isocoumarinyl, chromonyl, chromanonyl,
 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl,
 dihydroisoquinolinonyl, dihydrocoumarinyl,
 dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl,
 benzoxazolinonyl, pyridinyl-N-oxide, pyrrolyl N-oxide,
 10 pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide,
 quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide,
 isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-
 oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-
 oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-
 15 oxide, indazolyl N-oxide, benzothiazolyl N-oxide,
 benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide,
 thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide,
 benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide,

where the R_1 -heteroaryl group is bonded to $-(CH_2)_{n1}-$ by
 20 any ring atom of the parent R_N -heteroaryl group substituted by
 hydrogen such that the new bond to the R_1 -heteroaryl group
 replaces the hydrogen atom and its bond, where heteroaryl is
 optionally substituted with one, two, three, four, or five of:

(1) C_1 - C_6 alkyl optionally substituted with one, two
 25 or three substituents selected from the group consisting of C_1 -
 C_3 alkyl, -F, -Cl, -Br, -I, -OH,
 -SH, $-NR_{1-a}R_{1-b}$, $-C\equiv N$, $-CF_3$, and C_1 - C_3 alkoxy,

(2) C_2 - C_6 alkenyl with one or two double bonds,
 optionally substituted with one, two or three substituents
 30 selected from the group consisting of -F, -Cl, -OH, -SH, $-C\equiv N$,
 $-CF_3$, C_1 - C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(3) C_2 - C_6 alkynyl with one or two triple bonds,
 optionally substituted with one, two or three substituents

selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(4) -F, -Cl, -Br and -I,

(5) -C₁-C₆ haloalkoxy,

5 (6) -C₁-C₆ alkoxy

(7) -NR_{N-2}R_{N-3},

(8) -OH,

(9) -C≡N,

(10) C₃-C₇ cycloalkyl, optionally substituted with
 10 one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(11) -CO-(C₁-C₄ alkyl),

(12) -SO₂-NR_{1-a}R_{1-b},

15 (13) -CO-NR_{1-a}R_{1-b},

(14) -SO₂-(C₁-C₄ alkyl), with the proviso that when n₁ is zero R_{1-heteroaryl} is not bonded to the carbon chain by nitrogen,

(VIII) -(CH₂)_{n1}-(R_{1-heterocycle}) where n₁ is as defined above
 20 and R_{1-heterocycle} is selected from the group consisting of morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,
 25 homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide,
 30 dithianyl, pyranyl, dihydrofuranyl, pyrrolidinonyl, imidazolidinonyl, imidazolidinondionyl, wherein each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring, and

where the R_1 -heterocycle group is bonded by any atom of the parent R_1 -heterocycle group substituted by hydrogen such that the new bond to the R_1 -heterocycle group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with

5 one, two, three or four:

(1) C_1 - C_6 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, - $NR_{1-a}R_{1-b}$, -C \equiv N, -CF₃, and C_1 - C_3 alkoxy,

10 (2) C_2 - C_6 alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C \equiv N, -CF₃, C_1 - C_3 alkoxy, - $NR_{1-a}R_{1-b}$,

(3) C_2 - C_6 alkynyl optionally substituted with one, two or three substituents independently selected from the group
15 consisting of -F, -Cl, -OH, -SH, -C \equiv N, -CF₃, C_1 - C_3 alkoxy, and - $NR_{1-a}R_{1-b}$,

(4) -F, -Cl, -Br and -I,

(5) C_1 - C_6 alkoxy,

(6) - C_1 - C_6 haloalkoxy,

20 (7) - $NR_{N-2}R_{N-3}$,

(8) -OH,

(9) -C \equiv N,

(10) C_3 - C_7 cycloalkyl, optionally substituted with one, two or three substituents independently selected from the
25 group consisting of -F, -Cl, -OH, -SH
-C \equiv N, -CF₃, C_1 - C_3 alkoxy, and - $NR_{1-a}R_{1-b}$,

(11) -CO-(C_1 - C_4 alkyl),

(12) -SO₂- $NR_{1-a}R_{1-b}$,

(13) -CO- $NR_{1-a}R_{1-b}$,

30 (14) -SO₂-(C_1 - C_4 alkyl),

(15) =O, with the proviso that when n_1 is zero R_1 -heterocycle is not bonded to the carbon chain by nitrogen;

where R_2 is selected from the group consisting of:

(I) -H,

(II) C₁-C₆ alkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

5 (III) -(CH₂)₀₋₄-R₃₀ where R₃₀ is R₁-aryl, R₁-heteroaryl, or R₁-heterocycle

(IV) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of
10 -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(V) C₂-C₆ alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

15 (VI) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},
where R₃ is selected from the group consisting of:

20 (I) -H,

(II) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

25 (III) -(CH₂)₀₋₄-R₃₀,

(IV) C₂-C₆ alkenyl,

(V) C₂-C₆ alkynyl,

(VI) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents independently selected from
30 the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

or R₂ and R₃ are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six,

and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, -NR_{N-2}-;

R_N is:

- 5 (I) R_{N-1}-X_N- where X_N is selected from the group consisting of:

- (A) -CO-,
(B) -SO₂-,
(C) -(CR'R'')₁₋₆ wherein

10 R' and R'' at each occurrence are the same or different and are -H, C₁-C₄ alkyl, phenyl, or pyridyl

(D) -CO-(CR'R'')₁₋₆-X_{N-1} wherein X_{N-1} is selected from the group consisting of -O-, -S- and -NR'-,

(E) a single bond, and

15 (F) -CO-(CR'R'')₁₋₆-

where R_{N-1} is selected from the group consisting of:

(A) R_{N-aryl} wherein R_{N-aryl} at each occurrence is independently phenyl; naphthyl; tetralinyl; indanyl; indenyl; dihydronaphthyl; or 6,7,8,9-tetrahydro-5H-

20 benzo[a]cycloheptenyl; each of which is optionally substituted with 1, 2, or 3 groups that at each occurrence are independently:

(1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group
25 consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, wherein R_{1-a} and R_{1-b} at each occurrence are independently H or C₁-C₆ alkyl,

- (2) -OH,
(3) -NO₂,
30 (4) -F, -Cl, -Br, -I,
(5) -CO₂H,
(6) -C≡N,

(7) $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$ wherein at each occurrence R_{N-2} and R_{N-3} are the same or different and are selected from the group consisting of:

- (a) $-H$,
- 5 (b) $-C_1-C_8$ alkyl optionally substituted with one substituent selected from the group consisting of:
 - (i) $-OH$,
 - (ii) $-NR'R''$
 - (iii) phenyl,
 - 10 (c) $-C_1-C_8$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $-F$, $-Cl$, $-Br$, or $-I$,
 - (d) $-C_3-C_8$ cycloalkyl,
 - (e) $-(C_1-C_2 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$,
 - 15 (f) $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$,
 - (g) $-C_2-C_6$ alkenyl,
 - (h) $-C_2-C_6$ alkynyl,
 - (i) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,
 - 20 (j) $-R_1\text{-aryl}$,
 - (k) $-R_1\text{-heteroaryl}$,
 - (l) $-R_1\text{-heterocycle}$, or
 - (m) R_{N-2} , R_{N-3} and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or
 - 25 heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, halo C_1-C_6 alkyl, halo C_1-C_6
 - 30 alkoxy, $-CN$, $-NO_2$, $-NH_2$, $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-OH$, $-C(O)NH_2$, $-C(O)NH(C_1-C_6 \text{ alkyl})$, $-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 thioalkoxy, and C_1-C_6 thioalkoxy C_1-C_6 alkyl;

(8) $-(CR'R'')_{0-4}CO-OR'$

- (B) $-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is selected from the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl,
- 5 phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indoliziny, indazolyl, benzisothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl,
- 10 naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranly, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranly, benzotetrahydrothienyl, purinyl,
- 15 benzodioxolyl, triazinyl, henoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl,
- 20 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyridinyl-N-oxide, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide,
- 25 quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indoliziny N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide,
- 30 benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide, imidazopyrazolyl, quinazolinonyl, pyrazopyridyl, benzooxadiazolyl, dihydropyrimidinonyl, and

dihydrobenzofuranonyl, where each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that
 5 the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:

(1) $C_1\text{-}C_6$ alkyl, optionally substituted with one, two or three substituents independently selected from the
 10 group consisting of $C_1\text{-}C_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, $C_1\text{-}C_3$ alkoxy, and -NR_{1-a}R_{1-b},

(2) -OH,

(3) -NO₂,

(4) -F, -Cl, -Br, -I,

15 (5) -CO₂H,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},

(8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),

(9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl),

20 (10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl),

(11) -(CH₂)₀₋₄-CO-(C₃-C₈ cycloalkyl),

(12) -(CH₂)₀₋₄-CO-R_{1-aryl},

(13) -(CH₂)₀₋₄-CO-R_{1-heteroaryl},

(14) -(CH₂)₀₋₄-CO-R_{1-heterocycle},

25 (15) -(CH₂)₀₋₄-CO-R_{N-4}

(16) -(CH₂)₀₋₄-CO₂-R_{N-5}

(17) -(CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3},

(18) -(CH₂)₀₋₄-SO-(aryl C₁-C₈ alkyl),

(19) -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl),

30 (20) -(CH₂)₀₋₄-SO₂-(C₃-C₈ cycloalkyl),

(21) -(CH₂)₀₋₄-N(H or R_{N-5})-CO-O-R_{N-5},

(22) -(CH₂)₀₋₄-N(H or R_{N-5})-CO-N(R_{N-5})₂,

(23) -(CH₂)₀₋₄-N-CS-N(R_{N-5})₂,

(24) -(CH₂)₀₋₄-N(-H or R_{N-5})-CO-R_{N-2},

- (25) $-(\text{CH}_2)_{0-4}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3},$
 (26) $-(\text{CH}_2)_{0-4}-\text{R}_{\text{N}-4},$
 (27) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl}),$
 (28) $-(\text{CH}_2)_{0-4}-\text{O}-\text{P}(\text{O})-(\text{OR}_{100})_2,$
 5 (29) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2,$
 (30) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2,$
 (31) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5}),$
 (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})-\text{COOH},$
 (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5}),$
 10 (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally}$
 substituted with one, two, three, four, or five of -F),
 (35) $\text{C}_3-\text{C}_8 \text{ cycloalkyl},$
 (36) $\text{C}_2-\text{C}_6 \text{ alkenyl optionally substituted with}$
 $\text{C}_1-\text{C}_3 \text{ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C}\equiv\text{N, -CF}_3, \text{C}_1-\text{C}_3$
 15 $\text{alkoxy, or -NR}_{1-a}\text{R}_{1-b},$
 (37) $\text{C}_2-\text{C}_6 \text{ alkynyl optionally substituted with}$
 $\text{C}_1-\text{C}_3 \text{ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C}\equiv\text{N, -CF}_3, \text{C}_1-\text{C}_3$
 $\text{alkoxy, or -NR}_{1-a}\text{R}_{1-b},$
 20 (38) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2},$
 (39) $-(\text{CH}_2)_{1-4}-\text{C}_3-\text{C}_8 \text{ cycloalkyl},$
 (C) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-aryl}},$
 (D) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}},$
 (E) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_1\text{-heterocycle},$
 (F) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-aryl}},$
 25 (G) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}},$
 (H) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_1\text{-heterocycle},$
 (I) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-aryl}},$
 (J) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-heteroaryl}},$
 (K) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_1\text{-heterocycle},$
 30 where W is
 (1) $-(\text{CH}_2)_{1-4}-,$
 (2) $-\text{O}-,$
 (3) $-\text{S}(\text{O})_{0-2}-,$
 (4) $-\text{N}(\text{R}_{\text{N}-5})-,$

(5) -CO-; or

(6) a bond;

(II) -CO-(C₁-C₁₀ alkyl) wherein the alkyl is optionally substituted with one two or three substituents independently

5 selected from the group consisting of:

(A) -OH,

(B) -C₁-C₆ alkoxy,

(C) -C₁-C₆ thioalkoxy,

(D) -CO₂-R_{N-8} where R_{N-8} at each occurrence is
 10 independently -H, C₁-C₆ alkyl or -phenyl which is optionally substituted with 1 or 2 groups that are independently halogen, C₁-C₄ alkoxy, C₁-C₄ alkyl or -C(O)NH₂,

(E) -CO-NR_{N-2}R_{N-3},

(F) -CO-R_{N-4},

15 (G) -SO₂-(C₁-C₈ alkyl),

(H) -SO₂-NR_{N-2}R_{N-3},

(I) -NH-CO-(C₁-C₆ alkyl),

(J) -NH-CO-O-R_{N-8},

(K) -NR_{N-2}R_{N-3},

20 (L) -R_{N-4},

(M) -O-CO-(C₁-C₆ alkyl),

(N) -O-CO-NR_{N-8}R_{N-8},

(O) -O-(C₁-C₅ alkyl)-COOH,

(P) -O-(C₁-C₆ alkyl optionally substituted with one,
 25 two, or three groups that are independently -F, -Cl, -Br, or -I),

(Q) -NH-SO₂-(C₁-C₆ alkyl),

(R) halogen,

(S) -N(H or R_{N-5})-SO₂-R_{N-2},

30 (T) -N(H or R_{N-5})-CO-(R_{N-2}), and

(U) -SO₂-R_{N-2},

(V) R_{N-aryl};

(III) $-\text{CO}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ wherein each alkyl is unsubstituted or independently substituted with one, two, or three substituents selected from the group consisting of :

- (A) $-\text{OH}$,
- 5 (B) $-\text{C}_1\text{-C}_6 \text{ alkoxy}$,
- (C) $-\text{C}_1\text{-C}_6 \text{ thioalkoxy}$,
- (D) $-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$,
- (E) $-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
- (F) $-\text{CO}-\text{R}_{\text{N}-4}$,
- 10 (G) $-\text{SO}_2-(\text{C}_1\text{-C}_8 \text{ alkyl})$,
- (H) $-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
- (I) $-\text{NH}-\text{CO}-(\text{C}_1\text{-C}_6 \text{ alkyl})$,
- (J) $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$,
- (K) $-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
- 15 (L) $-\text{R}_{\text{N}-4}$,
- (M) $-\text{O}-\text{CO}-(\text{C}_1\text{-C}_6 \text{ alkyl})$,
- (N) $-\text{O}-\text{CO}-\text{NR}_{\text{N}-8}\text{R}_{\text{N}-8}$,
- (O) $-\text{O}-(\text{C}_1\text{-C}_5 \text{ alkyl})-\text{CO}_2\text{H}$,
- (P) $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ optionally substituted with
- 20 one, two, or three groups that are independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$,
or $-\text{I}$),
- (Q) $-\text{NH}-\text{SO}_2-(\text{C}_1\text{-C}_6 \text{ alkyl})$,
- (R) halogen,
- (S) $-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$,
- 25 (T) $-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-(\text{R}_{\text{N}-2})$,
- (U) $-\text{SO}_2-\text{R}_{\text{N}-2}$, and
- (V) $\text{R}_{\text{N-aryl}}$;

(IV) $-\text{CO}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{S}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ wherein each alkyl is unsubstituted or substituted with one, two, or three of
30 substituents independently selected from the group consisting of:

- (A) $-\text{OH}$,
- (B) $-\text{C}_1\text{-C}_6 \text{ alkoxy}$,
- (C) $-\text{C}_1\text{-C}_6 \text{ thioalkoxy}$,

- (D) $-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$,
 (E) $-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
 (F) $-\text{CO}-\text{R}_{\text{N}-4}$,
 (G) $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$,
 5 (H) $-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
 (I) $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 (J) $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$,
 (K) $-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
 (L) $-\text{R}_{\text{N}-4}$,
 10 (M) $-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 (N) $-\text{O}-\text{CO}-\text{NR}_{\text{N}-8}\text{R}_{\text{N}-8}$,
 (O) $-\text{O}-(\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH}$,
 (P) $-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted with one, two, or three groups that are independently } -\text{F}, -\text{Cl}, -\text{Br}, \text{ or } -$
 15 I),
 (Q) $-\text{NH}-\text{SO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 (R) halogen,
 (S) $-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$,
 (T) $-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-(\text{R}_{\text{N}-2})$,
 20 (U) $-\text{SO}_2-\text{R}_{\text{N}-2}$, and
 (V) $\text{R}_{\text{N-aryl}}$;
 (V) $-\text{CO}-\text{CH}(-(\text{CH}_2)_{0-2}-\text{O}-\text{R}_{\text{N}-10})-(\text{CH}_2)_{0-2}-(\text{R}_{\text{N-aryl}} \text{ or } \text{R}_{\text{N-heteroaryl}})$

wherein

- $\text{R}_{\text{N}-10}$ is selected from the group consisting of:
 25 (1) $-\text{H}$,
 (2) $\text{C}_1-\text{C}_6 \text{ alkyl}$,
 (3) $\text{C}_3-\text{C}_8 \text{ cycloalkyl}$,
 (4) $\text{C}_2-\text{C}_6 \text{ alkenyl}$,
 (5) $\text{C}_2-\text{C}_6 \text{ alkynyl}$,
 30 (6) $\text{R}_{1-\text{aryl}}$,
 (7) $\text{R}_{\text{N-heteroaryl}}$,
 (8) $\text{R}_{\text{N-heterocycle}}$

(VI) $-\text{CO}-(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$ where the cycloalkyl group is optionally substituted with one or two substituents independently selected from the group consisting of:

- (A) $-(\text{CH}_2)_{0-4}\text{-OH}$,
- 5 (B) $-(\text{CH}_2)_{0-4}\text{-C}_1\text{-C}_6 \text{ alkoxy}$,
- (C) $-(\text{CH}_2)_{0-4}\text{-C}_1\text{-C}_6 \text{ thioalkoxy}$,
- (D) $-(\text{CH}_2)_{0-4}\text{-CO-O-R}_{\text{N-8}}$,
- (E) $-(\text{CH}_2)_{0-4}\text{-CO-NR}_{\text{N-2}}\text{R}_{\text{N-3}}$,
- (F) $-(\text{CH}_2)_{0-4}\text{-CO-R}_{\text{N-4}}$,
- 10 (G) $-(\text{CH}_2)_{0-4}\text{-SO}_2\text{-(C}_1\text{-C}_8 \text{ alkyl)}$,
- (H) $-(\text{CH}_2)_{0-4}\text{-SO}_2\text{-NR}_{\text{N-2}}\text{R}_{\text{N-3}}$,
- (I) $-(\text{CH}_2)_{0-4}\text{-NH-CO-(C}_1\text{-C}_6 \text{ alkyl)}$,
- (J) $-\text{NH-CO-O-R}_{\text{N-8}}$,
- (K) $-(\text{CH}_2)_{0-4}\text{-NR}_{\text{N-2}}\text{R}_{\text{N-3}}$,
- 15 (L) $-(\text{CH}_2)_{0-4}\text{-R}_{\text{N-4}}$,
- (M) $-\text{O-CO-(C}_1\text{-C}_6 \text{ alkyl)}$,
- (N) $-\text{O-CO-NR}_{\text{N-8}}\text{R}_{\text{N-8}}$,
- (O) $-\text{O-(C}_1\text{-C}_6 \text{ alkyl)-CO}_2\text{H}$,
- (P) $-\text{O-(C}_1\text{-C}_6 \text{ alkyl optionally substituted with one,}$
 20 $\text{two, or three groups that are independently selected from -F, -}$
 Cl, -Br, and -I) ,
- (Q) $-\text{NH-SO}_2\text{-(C}_1\text{-C}_6 \text{ alkyl)}$,
- (R) halogen,
- (S) $-\text{N(H or R}_{\text{N-5}})\text{-SO}_2\text{-R}_{\text{N-2}}$,
- 25 (T) $-\text{N(H or R}_{\text{N-5}})\text{-CO-(R}_{\text{N-2}})$,
- (U) $-\text{SO}_2\text{-R}_{\text{N-2}}$, and
- (V) $\text{R}_{\text{N-aryl}}$;

where R_C is:

- (I) $-\text{C}_1\text{-C}_{10} \text{ alkyl}$ optionally substituted with one, two or
 30 three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$
 $\text{alkyl, -F, -Cl, -Br, -I, -OH}$,

-SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b}, -OC=O NR_{1-a}R_{1-b}, -S(=O)₀₋₂ R_{1-a}, -NR_{1-a}C=O NR_{1-a}R_{1-b}, -C=O NR_{1-a}R_{1-b}, and -S(=O)₂ NR_{1-a}R_{1-b},

(II) -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl where cycloalkyl can be optionally substituted with one, two or three substituents independently selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -CO₂H, -CO₂-(C₁-C₄ alkyl), and -NR_{1-a}R_{1-b},

(III) -(CR_{C-x}R_{C-y})₀₋₄-R_{C-aryl} at each occurrence is independently phenyl; naphthyl; tetralinyl; indanyl; indenyl; dihydronaphthyl; or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl; each of which is optionally substituted with 1, 2, or 3 groups that at each occurrence are independently:

(1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(2) -OH,

(3) -NO₂,

(4) -F, -Cl, -Br, -I,

(5) -CO₂H,

(6) -C≡N, and

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3};

where R_{C-x} and R_{C-y} are independently

-H,

C₁-C₄ alkyl optionally substituted with one or two -OH,

C₁-C₄ alkoxy optionally substituted with 1, 2, or 3 -

F,

-(CH₂)₀₋₄-C₃-C₈ cycloalkyl,

C₂-C₆ alkenyl,

C₂-C₆ alkynyl, and

phenyl,

or R_{C-x} and R_{C-y} are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of
 5 -O-, -S-, -SO₂-, -NR_{N-2}- and R_{C-aryl} is defined as is defined above;

(IV) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heteroaryl} where R_{C-heteroaryl} at each occurrence is independently selected from the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl,
 10 indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzoisothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl,
 15 triazolyl, tetrazolyl, oxazolopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl,
 20 benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, hexoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoquinazolinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisoquinazolinyl, benzopyranyl, benzothiopyranyl,
 25 coumarinyl, isocoumarinyl, chromonyl, chromanonyl, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, imidazopyrazolyl, quinazolinonyl,
 30 pyrazopyridyl, benzooxadiazolyl, dihydropyrimidinonyl, dihydrobenzofuranonyl, pyridinyl-N-oxide, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-

oxide, phthalaziny N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indoliziny N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide,

where the R_C -heteroaryl group is bonded by any atom of the parent R_C -heteroaryl group substituted by hydrogen such that the new bond to the R_C -heteroaryl group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted 1, 2, 3, or 4 groups that are independently:

(1) C_1 - C_6 alkyl, optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C \equiv N, -CF $_3$, C_1 - C_3 alkoxy, and -NR $_{1-a}$ R $_{1-b}$,

(2) -OH,

(3) -NO $_2$,

(4) -F, -Cl, -Br, -I,

(5) -CO-OH,

(6) -C \equiv N,

(7) -(CH $_2$) $_{0-4}$ -CO-NR $_{N-2}$ R $_{N-3}$,

(8) -(CH $_2$) $_{0-4}$ -CO-(C_1 - C_{12} alkyl),

(9) -(CH $_2$) $_{0-4}$ -CO-(C_2 - C_{12} alkenyl),

(10) -(CH $_2$) $_{0-4}$ -CO-(C_2 - C_{12} alkynyl),

(11) -(CH $_2$) $_{0-4}$ -CO-(C_3 - C_7 cycloalkyl),

(12) -(CH $_2$) $_{0-4}$ -CO-R $_{1-aryl}$,

(13) -(CH $_2$) $_{0-4}$ -CO-R $_{1-heteroaryl}$,

(14) -(CH $_2$) $_{0-4}$ -CO-R $_{1-heterocycle}$,

(15) -(CH $_2$) $_{0-4}$ -CO-R $_{N-4}$,

(16) -(CH $_2$) $_{0-4}$ -CO-O-R $_{N-5}$,

(17) -(CH $_2$) $_{0-4}$ -SO $_2$ -NR $_{N-2}$ R $_{N-3}$,

(18) -(CH $_2$) $_{0-4}$ -SO-(C_1 - C_8 alkyl),

(19) -(CH $_2$) $_{0-4}$ -SO $_2$ -(C_1 - C_{12} alkyl),

(20) -(CH $_2$) $_{0-4}$ -SO $_2$ -(C_3 - C_7 cycloalkyl),

- (21) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-\text{O}-\text{R}_{\text{N}-5},$
 (22) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2,$
 (23) $-(\text{CH}_2)_{0-4}-\text{N}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2,$
 (24) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or } \text{R}_{\text{N}-5})-\text{CO}-\text{R}_{\text{N}-2},$
 5 (25) $-(\text{CH}_2)_{0-4}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3},$
 (26) $-(\text{CH}_2)_{0-4}-\text{R}_{\text{N}-4},$
 (27) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl}),$
 (28) $-(\text{CH}_2)_{0-4}-\text{O}-\text{P}(\text{O})-(\text{OR}_{100})_2,$
 (29) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2,$
 10 (30) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2,$
 (31) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5}),$
 (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})-\text{COOH},$
 (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5}),$
 (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted}$
 15 $\text{with one, two, three, four, or five of } -\text{F}),$
 (35) $\text{C}_3-\text{C}_8 \text{ cycloalkyl},$
 (36) $\text{C}_2-\text{C}_6 \text{ alkenyl optionally substituted with } \text{C}_1-\text{C}_3$
 $\text{alkyl, } -\text{F}, -\text{Cl}, -\text{Br}, -\text{I}, -\text{OH}, -\text{SH}, -\text{C}\equiv\text{N}, -\text{CF}_3, \text{C}_1-\text{C}_3 \text{ alkoxy, or}$
 $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}},$
 20 (37) $\text{C}_2-\text{C}_6 \text{ alkynyl optionally substituted with } \text{C}_1-\text{C}_3$
 $\text{alkyl, } -\text{F}, -\text{Cl}, -\text{Br}, -\text{I}, -\text{OH}, -\text{SH}, -\text{C}\equiv\text{N}, -\text{CF}_3, \text{C}_1-\text{C}_3 \text{ alkoxy, or}$
 $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}},$
 (38) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}, \text{ and}$
 (39) $-(\text{CH}_2)_{1-4}-(\text{C}_3-\text{C}_8 \text{ cycloalkyl}),$
 25 (V) $-(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}-\text{aryl}-\text{R}_{\text{C}}-\text{aryl},$
 (VI) $-(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}-\text{aryl}-\text{R}_{\text{C}}-\text{heteroaryl},$
 (VII) $-(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}-\text{heteroaryl}-\text{R}_{\text{C}}-\text{aryl},$
 (VIII) $-(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}-\text{heteroaryl}-\text{R}_{\text{C}}-\text{heteroaryl},$
 (IX) $-(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}-\text{aryl}-\text{R}_{\text{C}}-\text{heterocycle}, \text{ wherein}$
 30 $\text{R}_{\text{C}}-\text{heterocycle}$ is selected from the group consisting of
 $\text{morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide,}$
 $\text{thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl,}$
 $\text{pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl,}$
 $\text{tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,}$

homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, 5 tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide, dithianyl, pyranyl, dihydrofuranyl, pyrrolidinonyl, imidazolidinonyl, imidazolidinondionyl, wherein each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring, and

10 where the R_1 -heterocycle group is bonded by any atom of the parent R_1 -heterocycle group substituted by hydrogen such that the new bond to the R_1 -heterocycle group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three or four:

15 (1) C_1 - C_6 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, - $NR_{1-a}R_{1-b}$, -C \equiv N, -CF₃, and C_1 - C_3 alkoxy,

(2) C_2 - C_6 alkenyl optionally substituted with one, 20 two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C \equiv N, -CF₃, C_1 - C_3 alkoxy, - $NR_{1-a}R_{1-b}$,

(3) C_2 - C_6 alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C \equiv N, -CF₃, C_1 - C_3 alkoxy, and - 25 $NR_{1-a}R_{1-b}$,

(4) -F, -Cl, -Br and -I,

(5) C_1 - C_6 alkoxy,

(6) - C_1 - C_6 haloalkoxy,

(7) - $NR_{N-2}R_{N-3}$,

30 (8) -OH,

(9) -C \equiv N,

(10) C_3 - C_7 cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH

-C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b},

(11) -CO-(C₁-C₄ alkyl),

(12) -SO₂-NR_{1-a}R_{1-b},

(13) -CO-NR_{1-a}R_{1-b},

5 (14) -SO₂-(C₁-C₄ alkyl),

(15) =O, with the proviso that when n₁ is zero R₁-

heterocycle is not bonded to the carbon chain by nitrogen;

(X) -(CR_{C-x}R_{C-y})₀₋₄-R_C-heteroaryl-R_C-heterocycle,

(XI) -(CR_{C-x}R_{C-y})₀₋₄-R_C-heterocycle-R_C-aryl,

10 (XII) -(CR_{C-x}R_{C-y})₀₋₄-R_C-heterocycle-R_C-heteroaryl,

(XIII) -(CR_{C-x}R_{C-y})₀₋₄-R_C-heterocycle-R_C-heterocycle,

(XIV) -(CR_{C-x}R_{C-y})₀₋₄-R_C-heterocycle,

(XV) -[C(R_{C-1})(R_{C-2})]₁₋₃-CO-N-(R_{C-3})₂ where R_{C-1} and R_{C-2} are the same or different and are selected from the group

15 consisting of:

(A) -H,

(B) -C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH,

20 -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, and -NR_{1-a}R₁,

(C) C₂-C₆ alkenyl optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, and -NR_{1-a}R_{1-b},

25 (D) C₂-C₆ alkynyl optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, and -NR_{1-a}R_{1-b},

(E) -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl),

30 (F) -(CH₂)₀₋₄-C₃-C₈ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, and -NR_{1-a}R_{1-b}

(G) -(C₁-C₄ alkyl)-R_C-aryl,

(H) $-(C_1-C_4 \text{ alkyl})-R_C\text{-heteroaryl}$,

(I) $-(C_1-C_4 \text{ alkyl})-R_C\text{-heterocycle}$,

(J) $-R_C\text{-heteroaryl}$,

(K) $-R_C\text{-heterocycle}$,

5 (M) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_C\text{-aryl}$ where R_{C-4} is $-O-$, $-S-$

or

$-NR_{C-5}-$ where R_{C-5} is C_1-C_6 alkyl,

(N) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_C\text{-heteroaryl}$,

(O) $-R_C\text{-aryl}$,

10 and where R_{C-3} at each occurrence is the same or different and is:

(A) $-H$,

(B) $-C_1-C_6$ alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O\text{-phenyl}$, and $-NR_{1-a}R_{1-b}$,

(C) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O\text{-phenyl}$, and $-NR_{1-a}R_{1-b}$,

(D) C_2-C_6 alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O\text{-phenyl}$, and $-NR_{1-a}R_{1-b}$,

(E) $-(CH_2)_{0-4}-C_3-C_8$ cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O\text{-phenyl}$, $-NR_{1-a}R_{1-b}$,

30 (F) $-R_C\text{-aryl}$,

(G) $-R_C\text{-heteroaryl}$,

(H) $-R_C\text{-heterocycle}$,

(I) $-(C_1-C_4 \text{ alkyl})-R_C\text{-aryl}$,

J) $-(C_1-C_4 \text{ alkyl})-R_C\text{-heteroaryl}$,

(K) $-(C_1-C_4 \text{ alkyl})-R_C\text{-heterocycle}$,

(XVI) $-\text{CH}(R_C\text{-aryl})_2$,

(XVII) $-\text{CH}(R_C\text{-heteroaryl})_2$,

(XVIII) $-\text{CH}(R_C\text{-aryl})(R_C\text{-heteroaryl})$,

5 (XIX) $-\text{cyclopentyl}$, $-\text{cyclohexyl}$, or $-\text{cycloheptyl}$ ring fused to $R_C\text{-aryl}$ or $R_C\text{-heteroaryl}$ or $R_C\text{-heterocycle}$, where one carbon of cyclopentyl, cyclohexyl, or $-\text{cycloheptyl}$ is optionally replaced with NH , NR_{N-5} , O , $\text{S}(=\text{O})_{0-2}$, and where cyclopentyl, cyclohexyl, or $-\text{cycloheptyl}$ can be optionally substituted with one or two -
 10 C_1-C_3 alkyl, $-\text{F}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $=\text{O}$, and $-\text{NR}_{1-a}\text{R}_{1-b}$,

(XX) C_2-C_{10} alkenyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O}$ -
 15 phenyl, and $-\text{NR}_{1-a}\text{R}_{1-b}$,

(XXI) C_2-C_{10} alkynyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O}$ -phenyl, and $-\text{NR}_{1-a}\text{R}_{1-b}$,

20 (XXI) $-(\text{CH}_2)_{0-1}-\text{CHR}_{C-6}-(\text{CH}_2)_{0-1}-R_C\text{-aryl}$ where R_{C-6} is $-(\text{CH}_2)_{0-6}-\text{OH}$,

(XXII) $-(\text{CH}_2)_{0-1}-\text{CHR}_{C-6}-(\text{CH}_2)_{0-1}-R_C\text{-heteroaryl}$,

(XXIII) $-\text{CH}(-R_C\text{-aryl} \text{ or } R_C\text{-heteroaryl})-\text{CO}_2(C_1-C_4 \text{ alkyl})$,

(XXIV) $-\text{CH}(-\text{CH}_2-\text{OH})-\text{CH}(-\text{OH})-\text{NO}_2$,

25 (XXV) $(C_1-C_6 \text{ alkyl})-\text{O}-(C_1-C_6 \text{ alkyl})-\text{OH}$,

(XXVII) $-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}(-\text{O}-\text{CH}_2-\text{CH}_3)_2$,

(XXVIII) $-\text{H}$,

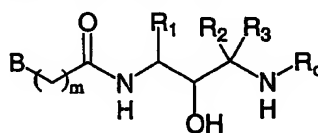
(XXIX) $-(\text{CH}_2)_{0-6}-\text{C}(=\text{NR}_{1-a})(\text{NR}_{1-a}\text{R}_{1-b})$;

R_{25} at each occurrence is independently selected from the
 30 group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, halo C_1-C_6 alkyl, C_1-C_6 alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, and NH_2 , and $-\text{R}_{26}-\text{R}_{27}$, wherein

R_{26} is selected from the group consisting of $-C(O)-$, $-SO_2-$, $-CO_2-$, $-C(O)NH-$, and $-C(O)N(C_1-C_6 \text{ alkyl})-$;

R_{27} is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl C_1-C_6 alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, haloalkyl, hydroxyalkyl, $-C(O)NH_2$, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-C(O)NH(C_1-C_6 \text{ alkyl})$, $-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$.

2. A compound of the formula



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and pharmaceutically acceptable salts thereof wherein m is 0-5;

B is aryl or heteroaryl optionally substituted with one or two groups independently selected from R_6 , R'_6 , R''_6 and R'''_6 , or

B is cycloalkyl or heterocycloalkyl optionally substituted with one, two, three, four, five, six, seven or eight groups independently selected from R_{6a} , R_{6b} , R'_{6a} , R'_{6b} , R''_{6a} , R''_{6b} , R'''_{6a} and R'''_{6b} ;

C_1-C_8 alkyl, C_2-C_7 alkenyl or C_2-C_7 alkynyl, each of which is optionally substituted with one, two or three groups selected from $-NRR'$, $-SR$, $-CN$, $-OCF_3$, $-CF_3$, $-CONRR'$, $-CO_2R$, $-SO_2NRR'$, $-O-P(=O)(OR)(OR')$, $-N(R)-C(=O)(R')$, $-N(R)(SO_2R')$, $-SO_2R$, $-C(=O)R$, $-NO_2$, halogen, $-(CH_2)_{0-4}$ -aryl, and $-(CH_2)_{0-4}$ -heteroaryl, or

R and R' independently are $-H$, $-(C_1-C_{10})$ alkyl, $-(CH_2)_{0-4}$ - R_{aryl} , $-(CH_2)_{0-4}$ - $R_{\text{heteroaryl}}$, $-(CH_2)_{0-4}$ - $R_{\text{heterocyclyl}}$, or

C_2-C_7 alkenyl or C_2-C_7 alkynyl, each of which is optionally substituted with one, two or three substituents selected from the group consisting of halogen, $-OH$,

-SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, mono- or dialkylamino, and C₁-C₆ alkyl, or

5 -(CH₂)₀₋₄- C₃-C₇ cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, mono- or dialkylamino, and C₁-C₆ alkyl;

benzyl where the phenyl ring is optionally substituted with 1-3 groups independently selected from halogen,

10 -OH, -SH, -C≡N, mono or dialkylamino, C₁-C₆ alkoxy, or trifluoromethyl;

R₆, R'₆, R''₆, R'''₆, R_{6a}, R_{6b}, R'_{6a}, R'_{6b}, R''_{6a}, R''_{6b}, R'''_{6a} and R'''_{6b} independently are -OR, -NO₂, halogen, -CO₂R, -C≡N, -NRR', -SR, -SO₂R, -C(=O)R, -OCF₃, -CF₃, -CONRR', -SO₂NRR',

15 -O-P(=O)(OR)(OR'), -N(R)(COR'), -N(R)(SO₂R'), -(CH₂)₀₋₄-CO-NR₇R'₇, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONRR', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R_{aryl}, -(CH₂)₀₋₄-R_{heteroaryl}, -(CH₂)₀₋₄-R_{heterocyclyl}, -(CH₂)₀₋₄-CO-R_{aryl},

20 -(CH₂)₀₋₄-CO-R_{heteroaryl}, -(CH₂)₀₋₄-CO-R_{heterocyclyl}, -(CH₂)₀₋₄-CO-R₁₀, -(CH₂)₀₋₄-CO-O-R₁₁, -(CH₂)₀₋₄-SO₂-NR₇R'₇, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(H or R₁₁)-CO-O-R₁₁, -(CH₂)₀₋₄-N(H or R₁₁)-CO-N(R₁₁)₂, -(CH₂)₀₋₄-N(H or R₁₁)-CS-N(R₁₁)₂, -(CH₂)₀₋₄-N(H or R₁₁)-CO-R₇, -(CH₂)₀₋₄-NR₇R'₇, -(CH₂)₀₋₄-R₁₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(=O)(O-R_{aryl})₂, -(CH₂)₀₋₄-O-CO-N(R₁₁)₂, -(CH₂)₀₋₄-O-CS-N(R₁₁)₂, -(CH₂)₀₋₄-O-(R₁₁), -(CH₂)₀₋₄-O-(R₁₁)-COOH, -(CH₂)₀₋₄-S-(R₁₁), C₃-C₇ cycloalkyl, -(CH₂)₀₋₄-N(H or R₁₁)-SO₂-R₇, or -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, or

30 C₁-C₈ alkyl optionally substituted with one, two or three groups independently selected from C₁-C₆ alkyl, -F, -Cl, -Br, -I, -OR, -NO₂, -F, -Cl, -Br, -I, -CO₂R, -C≡N, -NRR', -SR, -SO₂R, -C(=O)R, -OCF₃, -CF₃, -CONRR', -SO₂NRR', -O-P(=O)(OR)(OR'), -N(R)(COR'), -

$N(R)(SO_2R')$, $-(CH_2)_{0-4}-CO-NR_7R'_7$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$
 alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-$
 C_{12} alkynyl), $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-}$
 $4-R_{ary1}$, $-(CH_2)_{0-4}-R_{heteroary1}$, $-(CH_2)_{0-4}-R_{heterocycl1}$, $-(CH_2)_{0-}$
 5 $4-CO-R_{ary1}$, $-(CH_2)_{0-4}-CO-R_{heteroary1}$, $-(CH_2)_{0-4}-CO-$
 $R_{heterocycl1}$, $-(CH_2)_{0-4}-CO-R_{10}$, $-(CH_2)_{0-4}-CO-O-R_{11}$, $-(CH_2)_{0-}$
 $4-SO_2-NR_7R'_7$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-$
 $(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl),
 $-(CH_2)_{0-4}-N(H$ or $R_{11})-CO-O-R_{11}$, $-(CH_2)_{0-4}-N(H$ or $R_{11})-CO-$
 10 $N(R_{11})_2$, $-(CH_2)_{0-4}-N(H$ or $R_{11})-CS-N(R_{11})_2$, $-(CH_2)_{0-4}-N(-H$
 or $R_{11})-CO-R_7$, $-(CH_2)_{0-4}-NR_7R'_7$, $-(CH_2)_{0-4}-R_{10}$, $-(CH_2)_{0-4}-$
 $O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(O-R_{ary1})_2$, $-(CH_2)_{0-}$
 $4-O-CO-N(R_{11})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{11})_2$, $-(CH_2)_{0-4}-O-(R_{11})$,
 $-(CH_2)_{0-4}-O-(R_{11})-COOH$, $-(CH_2)_{0-4}-S-(R_{11})$, C_3-C_7
 15 cycloalkyl, $-(CH_2)_{0-4}-N(-H$ or $R_{11})-SO_2-R_7$, or $-(CH_2)_{0-4}-$
 C_3-C_7 cycloalkyl, or
 C_2-C_7 alkenyl or C_2-C_7 alkynyl, each of which is
 optionally substituted with one, two or three
 groups independently selected from halogen or -
 20 OH, or
 C_2-C_7 alkenyl or C_2-C_7 alkynyl, each of which is optionally
 substituted with one, two or three groups
 independently selected from halogen, C_1-C_3 alkyl,
 $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, and mono-
 25 or dialkylamino, or
 $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl), where the alkyl portion is
 optionally substituted with one, two, three, four, or
 five of halogen, or
 any two of R_{6a} , R_{6b} , R'_{6a} , R'_{6b} , R''_{6a} , R''_{6b} , R'''_{6a} and R'''_{6b}
 30 together are oxo;
 R_7 and R'_7 are the same or different and represent $-H$, $-C_3-C_7$
 cycloalkyl, $-(C_1-C_2$ alkyl)- $(C_3-C_7$ cycloalkyl), $-(C_1-C_6$
 alkyl)- $O-(C_1-C_3$ alkyl), $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_1-$

C₆ alkyl chain with one double bond and one triple bond,
or
-C₁-C₆ alkyl optionally substituted with -OH or -NH₂; or;
-C₁-C₆ alkyl optionally substituted with one, two or three
5 groups independently selected from halogen; or
heterocyclyl optionally substituted with halogen, amino,
mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-
C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -
CO-NH₂, -CO-NH-C₁-C₆ alkyl, oxo and -CO-N(C₁-C₆
10 alkyl)₂; or
C₁-C₆ alkyl optionally substituted with one, two or
three groups independently selected from C₁-C₃
alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃
alkoxy, amino, and mono- or dialkylamino; or
15 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is
optionally substituted with one, two or three
groups independently selected from C₁-C₃ alkyl,
halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy,
amino, and mono- or dialkylamino; or
20 C₁-C₆ alkoxy optionally substituted with one, two or
three of halogen;
aryl or heteroaryl, each of which is optionally
substituted with halogen, amino, mono- or
dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆
25 alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-
NH₂, -CO-NH-C₁-C₆ alkyl, and -CO-N(C₁-C₆ alkyl)₂; or
C₁-C₆ alkyl optionally substituted with one, two or
three groups independently selected from C₁-C₃
alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃
30 alkoxy, amino, and mono- or dialkylamino; or
C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is
optionally substituted with one, two or three
groups independently selected from C₁-C₃ alkyl,

- halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or
C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;
- 5 R₁₀ is heterocyclyl optionally substituted with one, two, three or four groups independently selected from C₁-C₆ alkyl;
R₁₁ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(CH₂)₀₋₂-R_{aryl}, or -(CH₂)₀₋₂-R_{heteroaryl};
R_{aryl} is aryl optionally substituted with halogen, amino, mono-
10 or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂; or
C₁-C₆ alkyl optionally substituted with one, two or three groups independently selected from C₁-C₃ alkyl,
15 halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or
C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C₁-C₃ alkyl, halogen, -
20 OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or
C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;
- R_{heteroaryl} is heteroaryl, each of which is optionally substituted
25 with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂; or
C₁-C₆ alkyl optionally substituted with one, two or three
30 groups independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or

C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;

R_{heterocyclyl} is heterocyclyl optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, =O or -CO-N(C₁-C₆ alkyl)₂; or C₁-C₆ alkyl optionally substituted with one, two or three groups independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or

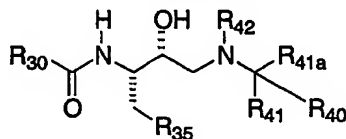
C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino; or

C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;

R₂ and R₃ are independently hydrogen or C₁-C₆ alkyl; or R₂ and R₃ taken together with the carbon atom to which they are attached form a 3 or 4-membered ring;

R_c is hydrogen or phenyl optionally substituted with C₁-C₃ alkyl, C₂-C₄ alkynyl, trifluoromethyl, or C₁-C₂ alkoxy.

3. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R₃₀ is selected from the group consisting of phenyl,
pyrazolopyrimidinyl, oxa-aza-benzoazulenyl, isoxazolyl,
triazolopyridinyl, pyrrolidinonyl, tetrahydrothia-aza-
fluorenyl, pyridyl, piperidinyl,
5 dihydrocyclopentaquinolinyl, furyl, naphthothienyl,
phthalazinonyl, thiadiazolyl, thienopyrimidinonyl, oxa-
diazacyclopentanaphthalenyl, dihydrobenzodioxepinyl,
chromanonyl, chromenonyl, oxazolidinyl, benzophenone,
pyrazinyl mono N-oxide, benzofuranyl, pyrazolyl,
10 -isoxazolyl-phenyl, phenyl-triazolyl, benzimidazolyl,
indolyl, phenyl-pyrrolyl, chromanyl, isoquinolinyl, -
thienyl-thienyl, benzothienyl, -phenyl-thiadiazolyl,
chromanonyl, quinolinyl, -pyrrolyl-C(O)-phenyl, -phenyl-O-
phenyl, -phenyl-oxazolyl, -pyrrolidinonyl-phenyl, -phenyl-
15 pyrimidinyl, -phenyl-oxadiazolyl, bicyclo[2.2.1]heptenyl,
cyclopentyl, thieno[2,3-b]thiophene, cyclohexyl, -phenyl-
imidazolyl, benzoxazole; dihydro-1H-indolyl; 2,3-dihydro-
benzo[b]thiophene 1,1-dioxide; benzo[b]thiophene 1,1-
dioxide; 2,3-dihydro-benzo[d]isothiazole 1,1-dioxide; -
20 phenyl-thiazolyl; -phenyl-pyrazolyl, -phenyl-C(O)-
piperidyl, -phenyl-C(O)-pyrrolidinyl, -phenyl-isoxazolyl,
isoindolyl, purinyl, oxazolyl, thiazolyl, pyridazinonyl,
thiazolyl, pyranyl, dihydropyranopyridinyl, diazepanyl,
azepanyl, cyclopropyl, dihydronaphthoisoxazolyl,
25 benzoindazolyl, dihydrocyclopentachromenonyl,
imidazopyrazolyl, tetrahydrocyclopentachromenonyl,
dihydroquinolinonyl, pyridyl N-oxide, isochromanyl,
quinazolinonyl, pyrazolopyrimidinyl, dihydrobenzothiophene
dioxide, dihydrofurobenzoisoxazolyl, dihydropyrimidine
30 dionyl, thienopyrazolyl, oxazolyl,
tetrahydrocyclopentapyrazolyl, dihydronaphthalenonyl,
dihydrobenzofuranonyl, dihydrocyclopentathienyl,
tetrahydrocyclopentapyrazolyl, tetrahydropyrazoloazepinyl,
indazolyl, tetrahydrocycloheptaisoxazolyl,

tetrahydroindolonyl, pyrrolidinyl, thienopyridinyl,
 dioxodihydrobenzothiazolonyl, triazolopyrimidinyl,
 thienyl, dihydrothienopyrimidinonyl, benzooxadiazolyl,
 carbazolyl, chromeno[3,4-d]isoxazolyl, chromanonyl,
 5 triazolopyridazinyl, oxazolidinyl, -pyrrolyl-(C₁-C₆
 alkyl)-pyridyl, -pyrrolyl-cyclohexyl, pyrrolidinonyl,
 dihydropyrazolyl, benzooxadiazolyl mono N-oxide, 1-H-
 pyridazinonyl, -phenyl-dihydro-1-H-pyrazolidinonyl, -
 phenyl-pyrrolidinyl dione, thienoindolyl,
 10 thioxobenzothiazolyl, pyrazolopyridinyl, thiomorpholinyl
 S-oxide, dihydrofurylbenzisoaxazolyl, benzoisothiazolinonyl
 1,1-dioxide; tetrahydropyrimidinyl dione,
 tetrahydrothiopyranylindolyl, benzodioxepinyl, -phenyl-
 pyrrazolidinonyl, dihydronaphthyl, tetrahydronaphthyl,
 15 isoindolinyl dione, -imidazole-benzyl, -thiene-
 dihydrooxazolyl, thienoquinolinyl, -pyrrolidine-phenyl,
 benzooxazolidinonyl, pyrrolopyridinyl, indanonyl, 1-H-
 imidazo[1,2-b]pyrazolyl, dihydrocyclopenta[b]thienyl,
 dihydroindazolonyl, tetrahydropyrazoloazepinyl,
 20 tetrahydrobenzofuranonyl, thienopyrazolyl,
 cyclopenta[c]pyrazolyl, tetrahydrocyclopenta[c]pyrazolyl,
 tetrahydroquinoxalinyl dione, tetrahydroindazolyl,
 imidazobenzoxazinyl, -phenyl-dihydropyrrolyl dione,
 -phenyl-O-benzyl, -phenyl-benzyl, 3',4'-dihydro-1'H-
 25 spiro[[1,3]dioxolane-2,2'-naphthalenyl, wherein each of
 the above is unsubstituted or substituted with 1, 2, 3, 4,
 or 5 groups that are independently selected from the group
 consisting of
 C₁-C₁₀ alkyl optionally substituted with 1 phenyl or 1 CN;
 30 OH, hydroxy C₁-C₁₀ alkyl optionally substituted with
 phenyl or (C₁-C₄ alkyl)phenyl, C₁-C₆ alkoxy optionally
 substituted with 1 or 2 groups that are independently
 hydroxy or phenyl; haloalkyl, haloalkoxy, (CH₂)₀-
₄C(O)NR₃₁R₃₂, -NR₃₁-SO₂-(C₁-C₆ alkyl) wherein the alkyl

group is optionally substituted with 1, 2, or 3
 groups that are independently halogen or R_{33} , $-SO_2-$
 $NH(C_1-C_6 \text{ alkyl})$ wherein the alkyl group is optionally
 substituted with 1 or 2 groups that are independently
 5 halogen, OH, alkoxy, or R_{33} ; $-(C_1-C_6 \text{ alkyl})-SO_2-(C_1-C_6$
 $\text{alkyl})$ wherein the alkyl group is optionally
 substituted with 1 or 2 groups that are independently
 halogen, OH, C_1-C_4 alkoxy, or R_{33} ; $-SO_2-(C_1-C_6 \text{ alkyl})$
 wherein the alkyl group is optionally substituted
 10 with 1 or 2 groups that are independently OH or C_1-C_4
 alkoxy , $-SO_2-N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ wherein each
 alkyl group is optionally substituted with 1 or 2
 groups that are independently halogen, OH or R_{33} ;
 $-SO_2-NH(C_1-C_6 \text{ alkyl})$ -phenyl wherein the phenyl is
 15 optionally substituted with 1 or 2 groups that are
 independently C_1-C_4 alkoxy or halogen, $-(C_1-C_6 \text{ alkyl})-$
 O -phenyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ -phenyl,
 triazolidine-3,5-dione, halogen, $-NHC(O)NH_2$,
 $-NHC(O)NH(C_1-C_6 \text{ alkyl})$, $-NHC(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6$
 20 $\text{alkyl})$, $-N(C_1-C_6 \text{ alkyl})C(O)NH_2$, $-N(C_1-C_6$
 $\text{alkyl})C(O)NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})C(O)N(C_1-C_6$
 $\text{alkyl})(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})$ thienyl, $-(C_1-C_6$
 $\text{alkyl})$ furanyl, $-S-(C_1-C_6 \text{ alkyl})$ phenyl, $-SO_2NR_{31}R_{32}$, $-$
 $C(O)-NR_{31}R_{32}$, $-NR_{31}R_{32}$, dithiane, $-NHC(S)NH_2$,
 25 $-NHC(S)NH(C_1-C_6 \text{ alkyl})$, $-NHC(S)N(C_1-C_6 \text{ alkyl})(C_1-C_6$
 $\text{alkyl})$, $-CO_2(C_1-C_6 \text{ alkyl})$, tetrahydropyran, phenyl
 optionally substituted with 1 or 2 groups that are
 independently F, Cl or Br; pyridine, $-C_2-C_4$ alkynyl-
 phenyl, $-O-C_3-C_8$ cycloalkyl, $-O-(C_1-C_6 \text{ alkyl})-R_{33}$;
 30 pyrrole optionally substituted with one or two methyl
 groups; 2,3-dihydro-benzofuran;
 benzo[1,2,5]oxadiazole, $-C(O)-(C_1-C_{10} \text{ alkyl})$ wherein
 the alkyl group is optionally substituted with NH_2 ,
 $N(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$; -

C(O)NH-phenyl, -C(O)N(C₁-C₆ alkyl)-phenyl, 4,4-
 dimethyl-4,5-dihydro-oxazole, -(C₁-C₆ alkyl)-S-
 pyridine, -(C₁-C₆ alkyl)-SO₂-pyridine, -(C₁-C₆
 thioalkoxy)-pyridine, thiazole optionally substituted
 5 with 1 or 2 methyl groups, pyrazole, -S-(C₁-C₆ alkyl)
 wherein the alkyl group is optionally substituted
 with 1 or 2 groups that are independently CN or OH;
 indole, (C₁-C₆ thioalkoxy)-(C₁-C₆ alkyl), C₂-C₈
 alkynyl, -(CH₂)₀₋₄-SO₂-(C₁-C₁₀ alkyl) wherein the alkyl
 10 group is optionally substituted with OH; -
 NHC(O)NH(C₃-C₈ cycloalkyl), -N(C₁-C₆ alkyl)C(O)NH(C₃-C₈
 cycloalkyl), -N(C₁-C₆ alkyl)C(O)N(C₁-C₆ alkyl)(C₃-C₈
 cycloalkyl), -NHC(O)N(C₁-C₆ alkyl)(C₃-C₈ cycloalkyl),
 -(C₁-C₆ alkoxy)-(C₁-C₆ thioalkoxy); -CO₂-(C₁-C₆ alkyl)
 15 wherein the alkyl group is optionally substituted
 with phenyl; -C(O)-furan; and imidazolyl;
 wherein R₃₁ and R₃₂ at each occurrence are independently
 selected from the group consisting of hydrogen, C₁-C₈
 alkyl, C₂-C₈ alkenyl, hydroxy C₁-C₆ alkyl, C₁-C₆
 20 haloalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, -(CH₂)₀₋₄-SO₂-(C₁-
 C₆ alkyl) wherein the alkyl is optionally substituted
 with 1, 2, 3 or 4 independently selected halogen
 atoms; -(CH₂)₀₋₄-SO₂-imidazolyl, -(C₁-C₆ alkyl)-
 C(O)NH₂, -(C₁-C₆ alkyl)-C(O)NH(C₁-C₆ alkyl), -(C₁-C₆
 25 alkyl)-C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-
 NH₂, -(C₁-C₆ alkyl)-NH(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-
 N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)phenyl,
 -(C₁-C₆ alkyl)pyridyl, -C(O)furanyl, (C₁-C₆ alkyl)-
 tetrahydrofuran, cyclopropyl, cyclobutyl,
 30 cyclopentyl, cyclohexyl, -CO₂-(C₁-C₆ alkyl), -(C₁-C₆
 alkyl)-furanyl, -(CH₂)₀₋₄-SO₂-thienyl, -pyrrolidinyl-
 benzyl, -(C₁-C₆ thioalkoxy)-(C₁-C₆ alkyl), -C(O)-(C₁-
 C₆ alkyl), (C₁-C₆ alkoxy), -(C₂-C₆ alkenyloxy), -(C₁-C₆

alkyl)-CO₂-(C₁-C₆ alkyl), and -C(O)-piperidinyl optionally substituted with C₁-C₆ alkyl; wherein the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, halogen, or

5 R₃₁, R₃₂ and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or a 6 membered heteroaryl ring, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with C₁-C₆ alkoxy, hydroxy, hydroxy C₁-C₆ alkyl, C₁-C₄ alkoxy C₁-C₆ alkyl, -C(O)NH₂, -C(O)NH-(C₁-C₆ alkyl)-phenyl;

10 R₃₃ at each occurrence is independently, H, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(phenyl), N(C₁-C₆ alkyl)(benzyl);

15 R₃₅ is phenyl, C₃-C₈ cycloalkyl, -S-phenyl, benzodioxole, thienyl, C₁-C₆ alkyl, furanyl, imidazolyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, OH, hydroxy C₁-C₆ alkyl, halogen, halo C₁-C₆ alkyl, halo C₁-C₆ alkoxy, -O-(C₁-C₆ alkyl)-phenyl, -CO₂-(C₁-C₆ alkyl), - (C₁-C₄ alkyl)-(C₅-C₆ cycloalkyl), or (CH₂)₀₋₄CN;

20 R₄₀ is phenyl, -phenyl-pyridyl, biphenyl, -phenyl-benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isoxazolyl, -C(O)-pyridyl, -(C₁-C₄ alkyl)-O-C(O)NH-phenyl wherein the phenyl is optionally substituted with 1, 2, or 3 halogen atoms; -(C₁-C₄ alkyl)-O-C(O)N(C₁-C₆ alkyl)-phenyl, -(C₁-C₆ alkyl)-phenyl, -(C₁-C₄ alkyl)-SO₂NH₂, - (C₁-C₄ alkyl)-SO₂NH(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-SO₂N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SO₂NH₂, -SO₂NH(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)(C₁-C₆ alkyl), CN, -(CH₂)₀₋₄-(C₃-C₈ cycloalkyl), - (C₁-C₄ alkyl)-C(O)O-(C₁-C₄ alkyl), -(C₁-C₄ alkyl)-R₃₃, C₁-C₁₀ alkyl, C₂-C₈ alkenyl, -(C₁-C₄ alkyl)-NHC(O)-(C₁-C₄ alkyl), -

25

30

$(\text{CH}_2)_{0-4}-\text{C}(\text{O})\text{NH}_2$, $-(\text{CH}_2)_{0-4}-\text{C}(\text{O})\text{NH}(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-(\text{CH}_2)_{0-4}-\text{C}(\text{O})\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_1-\text{C}_6 \text{ alkyl})$, naphthyl, tetrahydronaphthyl, dihydronaphthyl, $-(\text{CH}_2)_{0-4}-\text{imidazolyl}$, $-(\text{CH}_2)_{0-4}-\text{pyrrolidinyl}$, oxazolidinone 3,4-dihydro-
5 benzo[e][1,2]oxathiane 2,2-dioxide, pyrimidinyl, 3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide, pyridyl, or pyrimidyl, alkoxyalkyl, -phenyl-benzothienyl, -phenyl-cyclohexyl, -phenyl-cyclopentyl, -phenyl-(C_1-C_6 alkyl)-cyclopentyl, -phenyl-(C_1-C_6 alkyl)-cyclohexyl, -phenyl-oxazolyl, furanyl, tetrahydrofuranyl, 7-oxa-
10 bicyclo[2.2.1]heptyl; -dihydro-1-H-pyrazolidinone-phenyl; -phenyl-bicyclo[2.2.1] heptyl; imidazo[2,1-b][1,3]thiazolyl; azepanonyl; piperidinyl, $-(\text{C}_1-\text{C}_6 \text{ alkyl})$ -piperidinyl; bicyclo[2.2.1] heptyl; chromanonyl, $-(\text{C}_1-\text{C}_6 \text{ alkyl})$ -morpholinyl; -phenyl-C(O)-piperidinyl;
15 tetrahydrothiazolopyridinyl, -pyrrolo-C(O)-pyrrolidinyl; -phenyl-C(O)-phenyl; -phenyl-O-phenyl; -phenyl-O-benzyl; -phenyl-tetrahydropyridazinonyl; and -phenyl-dihydropyridazinonyl;
20 wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_8 alkyl optionally substituted with 1 or two groups that are independently CN or OH; C_1-C_6 alkoxy, halo (C_1-C_8 alkyl), halo (C_1-C_4 alkoxy), -O-
25 (C_1-C_4 alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, CN, -CHO, C_1-C_4 thioalkoxy, $-\text{NHSO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$ wherein the alkyl groups are optionally substituted with 1, 2, or 3 halogens; OH; $-\text{SO}_2\text{R}_{33}$;
30 R_{33} ; C_2-C_8 alkynyl; C_2-C_8 alkenyl; thioalkoxyalkyl; $-\text{SO}_2-(\text{C}_1-\text{C}_{10} \text{ alkyl})$; $-\text{NR}_{31}\text{R}_{32}$; $-\text{C}(\text{O})-\text{NR}_{31}\text{R}_{32}$; $-\text{OC}(\text{O})\text{R}_{33}$; C_1-C_8 alkanoyl; and $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{C}(\text{O})-(\text{C}_1-\text{C}_6 \text{ alkoxy})$, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_6 \text{ alkoxy})$; $-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{C}(\text{O})\text{NR}_{31}\text{R}_{32}$; $-\text{CO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$;

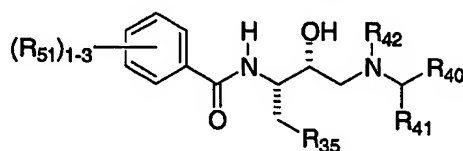
R_{41a} and R₄₁ are independently H, cyclohexyl, phenyl, or C₁-C₆ alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, C₁-C₄ thioalkoxy, C₁-C₄ thioalkoxy C₁-C₆ alkyl; or -C₁-C₆ alkyl-SO₂-C₁-C₆ alkyl;

- 5 R₄₀, R₄₁, and the atom to which they are attached form a C₃-C₈ cycloalkyl ring which is optionally substituted with C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, -CO₂NH₂, -CO₂NH(C₁-C₆ alkyl), or -CO₂N(C₁-C₆ alkyl)(C₁-C₆ alkyl); a thiazolyl ring which is optionally substituted with C₁-C₆ alkyl; isoxazolyl ring which is optionally substituted with C₁-C₆ alkyl; phenyl which is optionally substituted with 1, 2, or 3 groups that are independently halogen or C₁-C₆ alkyl; -pyrrolidinyl-benzyl; piperidinyl optionally substituted with 1 or 2 groups that are independently -CO₂-(C₁-C₆ alkyl) or -C(O)-(C₁-C₆ alkyl);

and

- R₄₂ is H, C₁-C₆ alkyl optionally substituted with OH; benzyl; -NHC(O)-(C₁-C₆ alkyl); -NHC(O)-phenyl wherein the phenyl is optionally substituted with 1 or 2 alkyl groups; -CO₂-(C₁-C₆ alkyl); -CO₂-(benzyl); or -C(O)-(C₁-C₆ alkyl).

4. A compound according to claim 3 of the formula



or a pharmaceutically acceptable salt thereof, wherein

- 25 R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH-SO₂-(C₁-C₄ alkyl) wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO₂-NH-(C₁-C₆ alkyl)-NH₂, -SO₂-NH-(C₁-C₆ alkyl)-NH(C₁-C₄ alkyl), -SO₂-NH-(C₁-C₆ alkyl)-N(C₁-C₄ alkyl)(C₁-C₄ alkyl), [1,2,4]triazolidine-3,5-dione, -NHC(O)NH₂, -NHC(O)NH(C₁-C₆ alkyl), -NHC(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆ alkyl)C(O)NH(C₁-C₆ alkyl), -N(C₁-C₆

alkyl)C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), halogen, -CF₃, OH,
-SO₂NR₃₁R₃₂, -C(O)NR₃₁R₃₂, -NR₃₁R₃₂, hydroxy C₁-C₁₀ alkyl
optionally substituted with phenyl or (C₁-C₄ alkyl)phenyl,
-O-(C₁-C₄ alkyl)-phenyl, -NHC(S)NH₂, -NHC(S)NH(C₁-C₆
5 alkyl), -NHC(S)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), (C₁-C₄ alkyl)-O-
phenyl, -C(O)-(C₁-C₆ alkyl) wherein the alkyl group is
optionally substituted with NH₂, N(C₁-C₆ alkyl), or N(C₁-C₆
alkyl)(C₁-C₆ alkyl); -O-C₃-C₆ cycloalkyl, oxazole
optionally substituted with 1, or 2 groups that are
10 independently C₁-C₄ alkyl or phenyl, hydroxy C₁-C₄ alkoxy,
aminoalkoxy, NH(C₁-C₆alkyl)-alkoxy, N(C₁-C₆alkyl)(C₁-
C₆alkyl)-alkoxy,
wherein R₃₁ and R₃₂ at each occurrence are independently
selected from the group consisting of hydrogen, C₁-C₆
15 alkyl, hydroxy C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(C₁-C₆
alkyl)-C(O)NH₂, -(C₁-C₆ alkyl)-C(O)NH(C₁-C₆ alkyl), -
(C₁-C₆ alkyl)-C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆
alkyl)-NH₂, -(C₁-C₆ alkyl)-NH(C₁-C₆ alkyl), -(C₁-C₆
alkyl)-N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆
20 alkyl)phenyl, -(C₁-C₆ alkyl)pyridyl, -C(O)furanyl,
(C₁-C₆ alkyl)-tetrahydrofuran, wherein
the phenyl and pyridyl groups are unsubstituted or
substituted with 1, 2, 3, 4, or 5 groups that
are independently C₁-C₄ alkyl, hydroxy, C₁-C₄
25 alkoxy, halogen, or
wherein at each occurrence R₃₁, R₃₂ and the nitrogen to
which they are attached independently form a
pyrrolidinyl, piperazinyl, piperidinyl, azepanyl,
pyridinyl, or pyrimidinyl ring, each of which is
30 optionally fused to a benzene, pyridine or pyrimidine
ring and each of which is optionally substituted with
C₁-C₆ alkoxy, C₁-C₆ alkyl, hydroxy, hydroxy C₁-C₆
alkyl, C₁-C₄ alkoxy C₁-C₆ alkyl, -C(O)NH₂, or -C(O)NH-
(C₁-C₆ alkyl)-phenyl.

5. A compound according to claim 4 wherein
 R₄₁ and R₄₂ are both hydrogen.

5 6. A compound according to claim 4 wherein
 R₃₅ is phenyl, cyclohexyl, -S-phenyl, benzodioxole, thienyl, C₃-
 C₆ alkyl, furanyl, each of which is unsubstituted or
 substituted with 1, 2, 3, 4, or 5 groups that are
 independently C₁-C₄ alkyl, C₁-C₄ alkoxy, OH, hydroxy C₁-C₆
 10 alkyl, halogen, halo C₁-C₆ alkyl, halo C₁-C₆ alkoxy, -O-
 (C₁-C₆ alkyl)-phenyl, -CO₂-(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-
 (C₅-C₆ cycloalkyl).

7. A compound according to claim 3 wherein
 15 R₃₅ is phenyl, cyclohexyl, -S-phenyl, benzodioxole, thienyl, C₃-
 C₆ alkyl, furanyl, each of which is unsubstituted or
 substituted with 1, 2, 3, 4, or 5 groups that are
 independently C₁-C₄ alkyl, C₁-C₄ alkoxy, OH, hydroxy C₁-C₆
 alkyl, halogen, halo C₁-C₆ alkyl, halo C₁-C₆ alkoxy, -O-
 20 (C₁-C₆ alkyl)-phenyl, -CO₂-(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-
 (C₅-C₆ cycloalkyl);

R₄₀ is phenyl, -phenyl-pyridine, biphenyl, -phenyl-
 benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-
 pyrimidinyl, -phenyl-isooxazolyl, -C(O)-pyridyl, -(C₁-C₄
 25 alkyl)-O-C(O)NH-phenyl, -(C₁-C₄ alkyl)-O-C(O)N(C₁-C₆
 alkyl)-phenyl, -(C₁-C₄ alkyl)-phenyl, -(C₁-C₄ alkyl)-SO₂NH₂,
 -(C₁-C₄ alkyl)-SO₂NH(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-SO₂N(C₁-C₆
 alkyl)(C₁-C₆ alkyl), CN, -(CH₂)₀₋₄-(C₃-C₈ cycloalkyl), -(C₁-
 C₄ alkyl)-C(O)O-(C₁-C₄ alkyl), -(C₁-C₄ alkyl)-R₃₃, C₁-C₈
 30 alkyl, -(C₁-C₄ alkyl)-NHC(O)-(C₁-C₄ alkyl), -(CH₂)₀₋₄-
 C(O)NH₂, -(CH₂)₀₋₄-C(O)NH(C₁-C₆ alkyl), -(CH₂)₀₋₄-C(O)N(C₁-C₆
 alkyl)(C₁-C₆ alkyl), tetrahydronaphthyl, dihydronaphthyl,
 wherein each of the above is unsubstituted or substituted
 with 1, 2, 3, 4, or 5 groups that are independently

- halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, halo (C₁-C₄ alkyl), -O-(C₁-C₄ alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, C₁-C₄ thioalkoxy, -NHSO₂-(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)SO₂-(C₁-C₄ alkyl)
- 5 wherein the alkyl groups are optionally substituted with 1, 2, or 3 halogens; OH, SO₂R₃₃, R₃₃;
- R₄₁ is H, cyclohexyl, phenyl, or C₁-C₆ alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C₁-C₄ thioalkoxy; and
- 10 R₄₂ is hydrogen or -CH₂CN.
8. A compound according to claim 6 wherein
- R₃₅ is phenyl, C₃-C₈ cycloalkyl, -S-phenyl, benzodioxole, thienyl, C₃-C₆ alkyl, furanyl, each of which is
- 15 unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, OH, hydroxy C₁-C₆ alkyl, halogen, CF₃, OCF₃, -Obenzyl, -CO₂-(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-(C₅-C₆ cycloalkyl);
- R₄₀ is phenyl, -phenyl-pyridine, biphenyl, -phenyl-
- 20 benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isoxazolyl, -C(O)-pyridyl, -(C₁-C₄ alkyl)-O-C(O)NH-phenyl, -(C₁-C₄ alkyl)-O-C(O)N(C₁-C₆ alkyl)-phenyl, -(C₁-C₄ alkyl)-phenyl, -(C₁-C₄ alkyl)-SO₂NH₂, -(C₁-C₄ alkyl)-SO₂NH(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-SO₂N(C₁-C₆ alkyl)(C₁-C₆ alkyl), CN, -(C₁-C₄ alkyl)-(C₃-C₆ cycloalkyl), -(C₁-C₄ alkyl)-C(O)O-(C₁-C₄ alkyl), -(C₁-C₄ alkyl)-R₃₃, C₁-C₈ alkyl, -(C₁-C₄ alkyl)-NHC(O)-(C₁-C₄ alkyl), -C(O)NH₂,
- 25 wherein each of the above rings is unsubstituted or substituted with 1, 2, or 3 groups that are independently
- 30 halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, -O-(C₁-C₄ alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, -NHSO₂-(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)SO₂-(C₁-C₄ alkyl) wherein the alkyl is optionally substituted with 1, 2, or 3 halogens,

- R_{41} is H, cyclohexyl, phenyl, or C_1 - C_6 alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C_1 - C_4 thioalkoxy; and
- R_{42} is hydrogen or $-CH_2CN$;
- 5 R_{51} at each occurrence is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-NHSO_2-(C_1-C_4 \text{ alkyl})$ wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, $-SO_2-NH-(C_1-C_6 \text{ alkyl})-NH_2$, $-SO_2-NH-(C_1-C_6 \text{ alkyl})-NH(C_1-C_4 \text{ alkyl})$, $-SO_2-NH-(C_1-C_6 \text{ alkyl})-N(C_1-C_4 \text{ alkyl})(C_1-C_4 \text{ alkyl})$,
- 10 $[1,2,4]\text{triazolidine-3,5-dione}$, $-NHC(O)NH_2$, $-NHC(O)NH(C_1-C_6 \text{ alkyl})$, $-NHC(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})C(O)NH_2$, $-N(C_1-C_6 \text{ alkyl})C(O)NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, halogen, $-CF_3$, OH, $-SO_2NR_{31}R_{32}$, $-C(O)NR_{31}R_{32}$, $-NR_{31}R_{32}$, hydroxy C_1 - C_{10} alkyl
- 15 optionally substituted with phenyl or 2-methylphenyl, $-O-(C_1-C_4 \text{ alkyl})$ -phenyl, $-NHC(S)NH_2$, $-NHC(S)NH(C_1-C_6 \text{ alkyl})$, $-NHC(S)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $(C_1-C_4 \text{ alkyl})$ -O-phenyl, $-C(O)-(C_1-C_6 \text{ alkyl})$ wherein the alkyl group is optionally substituted with NH_2 , $N(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$;
- 20 $-O-C_3-C_6$ cycloalkyl, oxazole optionally substituted with 1, or 2 groups that are independently C_1 - C_4 alkyl or phenyl, hydroxy C_1 - C_4 alkoxy, aminoalkoxy, $NH(C_1-C_6 \text{ alkyl})$ -alkoxy, $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ -alkoxy, wherein R_{31} and R_{32} at each occurrence are independently
- 25 selected from the group consisting of hydrogen, C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NH(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})$ phenyl, $-(C_1-C_6 \text{ alkyl})$ pyridyl, $-C(O)$ furanyl,
- 30 $(C_1-C_6 \text{ alkyl})$ -tetrahydrofuran, wherein the phenyl group is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1 - C_4 alkoxy, or halogen,

wherein at each occurrence R_{31} , R_{32} and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with hydroxy, C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, C_1 - C_4 alkoxy C_1 - C_6 alkyl, - $C(O)NH_2$, or - $C(O)NH$ -benzyl.

9. A compound according to claim 8 wherein

R_{35} is phenyl; halophenyl, dihalophenyl; trihalophenyl; tetrahalophenyl; pentahalophenyl; halo, benzyloxyphenyl; halo, alkylphenyl; benzyloxyphenyl; cyclohexyl; (C_1 - C_4 alkoxy)carbonylphenyl; (C_1 - C_4 alkoxy)phenyl; -S-phenyl, or benzodioxole;

R_{41} is H, cyclohexyl, phenyl, or C_1 - C_6 alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C_1 - C_4 thioalkoxy; and

R_{42} is hydrogen or $-CH_2CN$.

20

10. A compound according to claim 9 wherein

R_{35} is 3,5-dihalophenyl;

R_{40} is phenyl, -phenyl-pyridine, biphenyl, -phenyl-

benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isoxazolyl, -(C_1 - C_4 alkyl)-O- $C(O)NH$ -phenyl, -(C_1 - C_4 alkyl)-O- $C(O)N$ (C_1 - C_6 alkyl)-phenyl, -(C_1 - C_4 alkyl)- SO_2NH_2 , CN, -(C_1 - C_4 alkyl)-(C_3 - C_6 cycloalkyl), -(C_1 - C_4 alkyl)- $C(O)O$ -(C_1 - C_4 alkyl), -(C_1 - C_4 alkyl)- R_{33} , or C_1 - C_8 alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, CF_3 , -O-(C_1 - C_4 alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or - $NHSO_2$ -(C_1 - C_4 alkyl).

11. A compound according to claim 10 wherein
R₃₅ is 3,5-difluorophenyl; 3,5-dichlorophenyl; or 3-chloro,5-fluorophenyl; and
R₄₀ is phenyl which is unsubstituted or substituted with 1, 2,
5 or 3 groups that are independently fluoro, chloro, bromo, iodo, methyl, ethyl, methoxy, ethoxy, CF₃, or -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 groups that are independently halogen, or -NHSO₂CH₃.
- 10 12. A compound according to claim 11 wherein
R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, -NHSO₂CH₃, -SO₂-NH-(ethyl)-NH(CH₃), [1,2,4]triazolidine-3,5-dione, -NHC(O)NH₂, -CF₃, OH, -SO₂NR₃₁R₃₂, -C(O)NR₃₁R₃₂, hydroxyoctyl, -CH(OH)-2-methylphenyl, -Obenzyl, or -NHC(S)NH(CH₃);
15 wherein R₃₁ and R₃₂ at each occurrence are independently selected from the group consisting of hydrogen; C₁-C₆ alkyl; hydroxy C₁-C₆ alkyl; -(CH₂)C(O)N(CH₃)₂; -CH₂CH₂N(CH₃)₂; benzyl which is optionally substituted with 1 or 2 groups that are independently C₁-C₄
20 alkyl, C₁-C₄ alkoxy or halogen; phenethyl; -CH₂CH₂pyridyl; or -C(O)furanyl; or at each occurrence R₃₁, R₃₂ and the nitrogen to which they are attached independently form a pyrrolidiny, piperaziny, piperidiny, or azepany, each of which
25 is optionally substituted with hydroxymethyl, hydroxyethyl, methoxymethyl, or -C(O)NH₂.
- 30 13. A compound according to claim 12 wherein
R₄₀ is 3-ethylphenyl or 3-methoxyphenyl; and
R₄₂ is hydrogen.

14. A compound according to claim 12 wherein

R_{51} at each occurrence is independently H, $-SO_2NH$ -propyl-OH, $-SO_2NH$ -ethyl-OH, $-SO_2NH$ -ethyl-OCH₃, $-SO_2NH$ -CH(CH₃)₂-CH₂OH, $-SO_2NH$ -(CH₂CH(OH)CH₃), $-SO_2NH$ -ethyl-NH(CH₃), $-SO_2NH$ (CH₂CH₂OH)₂, $-SO_2NHCH$ (CH₃)CH₂OH, $-SO_2N$ (CH₃)₂, $-SO_2NH$ (CH₂CH(OH)CH₃), $-SO_2$ -pyrrolidine, $-SO_2$ -(2,6-dimethylpiperidine), $-SO_2$ -(2-propylpiperidine), $-SO_2$ -(hydroxypropyl), $-C(O)$ -(2-methoxymethylpyrrolidine), $-C(O)$ -(2-methylpyrrolidine), $-C(O)$ -(2,6-dimethylpyrrolidine), $-C(O)$ -(2-hydroxymethylpyrrolidine), $-C(O)N$ (methyl)(ethyl), $-C(O)N$ (methyl)(propyl), $-C(O)N$ (methyl)(butyl), $-C(O)N$ (propyl)(butyl), $-C(O)N$ (allyl)(cyclopentyl), $-C(O)N$ (allyl)(cyclohexyl), $-C(O)N$ (methyl)(methyl), $-C(O)N$ (ethyl)(ethyl), $-C(O)N$ (butyl)(butyl), $-C(O)N$ (isopropyl)(isopropyl), $-C(O)N$ (propyl)(propyl), $-C(O)N$ (methyl)(cyclohexyl), $-C(O)N$ (ethyl)(cyclohexyl), $-C(O)NH$ (cyclobutyl), $-C(O)NH$ (cyclopentyl), $-C(O)N$ (CH₃)(cyclopentyl), $-C(O)NH$ (2-methylcyclohexyl), $-C(O)NH$ (pentyl), $-C(O)N$ (pentyl)(pentyl), $-C(O)NH$ (isopentyl), $-C(O)NH$ (ethoxyethyl), $-C(O)N$ (CH₃)(methoxyethyl), $-C(O)N$ (propyl)(methoxyethyl), $-C(O)N$ (methoxyethyl)(methoxyethyl), $-C(O)N$ (ethoxyethyl)(ethoxyethyl), $-C(O)N$ (ethyl)(methoxyethyl), $-C(O)N$ (propyl)(hydroxyethyl), $-C(O)N$ (hydroxyethyl)(ethyl), ethynyl, methyl, bromo, $-N(CH_3)SO_2(CH_3)$, $-N(CH_3)SO_2$ -thienyl, $-N$ (hydroxypropyl)SO₂CH₃, $-CH_2-SO_2-(CH_3)$, or $-C(O)-CH(CH_3)CH_2CH_2CH_3$.

15. A compound according to claim 14 wherein there are two R_{51} groups.

16. A compound according to claim 15 wherein the R_{51} groups are at the 3 and 5 positions of the phenyl group.

17. A compound according to claim 11 wherein
R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆
alkoxy, -C(O)NR₃₁R₃₂, -C(O)CH₂NH₂, cyclopentyloxy, -
5 NHC(O)NH(ethyl), oxazole optionally substituted with 1 or
2 groups that are independently C₁-C₄ alkyl or phenyl,
hydroxyethoxy, diethylaminoethoxy,
wherein R₃₁ and R₃₂ at each occurrence are independently
selected from the group consisting of hydrogen, C₁-C₆
10 alkyl, hydroxy C₁-C₆ alkyl, -CH₂-tetrahydrofuran.

18. A compound according to claim 9 wherein
R₃₅ is cyclohexyl.

15 19. A compound according to claim 15 wherein
R₄₀ is phenyl, or C₁-C₈ alkyl, wherein each is unsubstituted or
substituted with 1, 2, 3, 4, or 5 groups that are
independently halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, halo (C₁-
C₄ alkyl); and
20 R₄₂ and R₄₁ are both hydrogen.

20. A compound according to claim 16 wherein
R₄₀ is phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-
ethoxyphenyl, 4-ethoxyphenyl, 3-trifluoromethylphenyl, 4-
25 trifluoromethylphenyl, 2-methylphenyl, 3-methylphenyl, 2-
ethylphenyl, 3-ethylphenyl, or C₃-C₆ alkyl; and
R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆
alkoxy, or halogen,
wherein R₃₁ and R₃₂ at each occurrence are independently
30 selected from the group consisting of hydrogen, C₁-C₆
alkyl, hydroxy C₁-C₆ alkyl, and -(C₁-C₆ alkyl)phenyl
wherein the phenyl group is unsubstituted or
substituted with 1, 2, or 3 groups that are
independently C₁-C₄ alkoxy, or halogen,

wherein at each occurrence R_{31} , R_{32} and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with hydroxy, hydroxy C_1 - C_6 alkyl, C_1 - C_4 alkoxy C_1 - C_6 alkyl, $-C(O)NH_2$, or $-C(O)NH$ -benzyl..

21. A compound according to claim 9 wherein R_{35} is 3-halo, 5-benzyloxyphenyl; 3-benzyloxyphenyl; or 4-benzyloxyphenyl; R_{41} is H, cyclohexyl, phenyl, or C_1 - C_6 alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C_1 - C_4 thioalkoxy; and R_{42} is hydrogen or $-CH_2CN$.

22. A compound according to claim 21 wherein R_{40} is phenyl, -phenyl-pyridine, biphenyl, $-(C_1-C_4 \text{ alkyl})-O-C(O)NH$ -phenyl, $-(C_1-C_4 \text{ alkyl})-O-C(O)N(C_1-C_6 \text{ alkyl})$ -phenyl, $-(C_1-C_4 \text{ alkyl})-SO_2NH_2$, $-(C_1-C_4 \text{ alkyl})-(C_3-C_6 \text{ cycloalkyl})$, $-(C_1-C_4 \text{ alkyl})-C(O)O-(C_1-C_4 \text{ alkyl})$, $-(C_1-C_4 \text{ alkyl})-R_{33}$, or C_1 - C_8 alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, CF_3 , -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or $-NHSO_2-(C_1-C_4 \text{ alkyl})$.

23. A compound according to claim 22 wherein R_{40} is phenyl or C_1 - C_8 alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, CF_3 , -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or $-NHSO_2-(C_1-C_4 \text{ alkyl})$; and

R₄₁ is hydrogen or C₁-C₆ alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C₁-C₄ thioalkoxy; R₄₂ is hydrogen; and

R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, -NHSO₂-(C₁-C₄ alkyl) wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO₂-NH-(C₁-C₆ alkyl)-NH₂, -SO₂-NH-(C₁-C₆ alkyl)-NH(C₁-C₄ alkyl), -SO₂-NH-(C₁-C₆ alkyl)-N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NHC(O)NH₂, -NHC(O)NH(C₁-C₆ alkyl), -NHC(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆ alkyl)C(O)NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), halogen, -CF₃, OH, -SO₂NR₃₁R₃₂, -C(O)NR₃₁R₃₂, -NR₃₁R₃₂, hydroxy C₁-C₁₀ alkyl, -Obenzyl, -NHC(S)NH₂, -NHC(S)NH(C₁-C₆ alkyl), -NHC(S)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), (C₁-C₄ alkyl)-O-phenyl, -C(O)-(C₁-C₆ alkyl), -O-cyclopentyl, -O-cyclohexyl, hydroxy C₁-C₄ alkoxy, aminoalkoxy, NH(C₁-C₆alkyl)-alkoxy, N(C₁-C₆alkyl)(C₁-C₆alkyl)-alkoxy, wherein R₃₁ and R₃₂ at each occurrence are independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -(C₁-C₆ alkyl)-NH(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-N(C₁-C₆ alkyl)(C₁-C₆ alkyl), and benzyl wherein the phenyl group is unsubstituted or substituted with 1, or 2 groups that are independently C₁-C₄ alkoxy, or halogen, wherein at each occurrence R₃₁, R₃₂ and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl, each of which is optionally substituted with hydroxy, hydroxy C₁-C₆ alkyl, C₁-C₄ alkoxy C₁-C₆ alkyl, -C(O)NH₂, or -C(O)NH-benzyl.

24. A compound according to claim 23 wherein

- R₄₀ is phenyl or C₁-C₈ alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, or CF₃; and
- 5 R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, -NHSO₂CH₃, -NHSO₂CF₃, halogen, -CF₃, OH, -SO₂NR₃₁R₃₂, -C(O)NR₃₁R₃₂, -NR₃₁R₃₂, hydroxy C₁-C₁₀ alkyl, hydroxy C₁-C₄ alkoxy, aminoalkoxy, NH(C₁-C₆alkyl)-alkoxy, N(C₁-C₆alkyl)(C₁-C₆alkyl)-alkoxy,
- 10 wherein R₃₁ and R₃₂ at each occurrence are independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, and benzyl wherein the phenyl group is unsubstituted or substituted with 1 or 2 groups that are independently methoxy, ethoxy,
- 15 or halogen, or wherein at each occurrence R₃₁, R₃₂ and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl ring each of which is optionally substituted with hydroxy,
- 20 hydroxy C₁-C₆ alkyl, C₁-C₄ alkoxy C₁-C₆ alkyl, or-C(O)NH₂.

25. A compound according to claim 24 wherein R₃₅ is 3-fluoro, 5-benzyloxyphenyl or 3-chloro, 5-benzyloxyphenyl.

25

26. A compound according to claim 9 wherein R₃₅ is -S-phenyl, benzo[1,3]dioxole, furanyl, or thienyl; R₄₁ is H, cyclohexyl, phenyl, or C₁-C₆ alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C₁-C₄ thioalkoxy; and

30 R₄₂ is hydrogen or -CH₂CN.

27. A compound according to claim 26 wherein

R₄₀ is phenyl, -phenyl-pyridine, biphenyl, -phenyl-pyrimidinyl, - (C₁-C₄ alkyl)-O-C(O)NH-phenyl, - (C₁-C₄ alkyl)-O-C(O)N(C₁-C₆ alkyl)-phenyl, - (C₁-C₄ alkyl)-SO₂NH₂, - (C₁-C₄ alkyl)-(C₃-C₆ cycloalkyl), - (C₁-C₄ alkyl)-C(O)O-(C₁-C₄ alkyl), - (C₁-C₄ alkyl)-R₃₃, or C₁-C₈ alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO₂-(C₁-C₄ alkyl), -NHSO₂CF₃.

10

28. A compound according to claim 27 wherein R₅₁ at each occurrence is independently selected from the group consisting of

C₁-C₄ alkyl, -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH₂,
-C(O)N(C₂-C₆ alkenyl)(C₃-C₈ cycloalkyl), -C(O)NH(C₃-C₈ cycloalkyl), -C(O)NH(C₁-C₆ alkyl), C(O)-(pyrrolidine) optionally substituted with 1 or two groups that are independently alkoxyalkyl or hydroxy, halogen, -C(O)N(C₁-C₆ hydroxyalkyl)(C₁-C₆ alkyl), -C(O)NH(alkoxyalkyl),
-C(O)N(alkoxyalkyl)(alkoxyalkyl), -C(O)N(C₁-C₆ alkyl)(alkoxyalkyl), -C(O)N(C₁-C₆ hydroxyalkyl)(alkyl), -NHSO₂CF₃, -N(C₁-C₆ alkyl)-SO₂-thienyl, -N(C₁-C₆ hydroxyalkyl)SO₂-(C₁-C₆ alkyl), -NHC(O)C₁-C₄ alkyl, oxazolyl optionally substituted with 1 or 2 methyl groups, thiazolyl optionally substituted with 1 or 2 methyl groups, pyrazolyl optionally substituted with 1 or 2 methyl groups, imidazolyl optionally substituted with 1 or 2 methyl groups, isoxazolyl optionally substituted with 1 or 2 methyl groups, pyrimidinyl optionally substituted with 1 or 2 methyl or halogen groups, -NHSO₂CH₃, -NHSO₂-imidazolyl wherein the imidazole ring is optionally substituted with 1 or 2 methyl groups, -N(C₁-C₆ alkyl)SO₂(C₁-C₆

alkyl), -SO₂NH-C₁-C₆ hydroxyalkyl, -SO₂NH-C₁-C₆ alkyl-NH(C₁-C₄ alkyl), -SO₂-piperazinyl optionally substituted with 1 or 2 methyl groups, -SO₂-pyrrolidine optionally substituted with 1 or 2 methyl groups, -SO₂-piperidine optionally substituted with 1 or 2 C₁-C₄ alkyl groups, -SO₂N(C₁-C₄ hydroxyalkyl)(C₁-C₄ hydroxyalkyl), -SO₂NH₂, -SO₂N(C₁-C₆ alkyl)(C₁-C₆ alkyl), C₂-C₆ alkynyl, -SO₂-(C₁-C₆ hydroxyalkyl), -SO₂NH(C₁-C₆ hydroxyalkyl), -SO₂N(C₁-C₆ alkyl)(C₁-C₆ hydroxyalkyl), -(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl), or -C(O)-(C₁-C₁₀ alkyl).

29. A compound according to claim 28 wherein R₅₁ at each occurrence is independently selected from the group consisting of -SO₂NH-propyl-OH, -SO₂NH-ethyl-OH, -SO₂NH-ethyl-OCH₃, -SO₂NH-CH(CH₃)₂-CH₂OH, -SO₂NH-(CH₂CH(OH)CH₃), -SO₂NH-ethyl-NH(CH₃), -SO₂NH-(CH₂CH₂OH)₂, -SO₂NHCH(CH₃)CH₂OH, -SO₂N(CH₃)₂, -SO₂NH(CH₂CH(OH)CH₃), -SO₂-pyrrolidine, -SO₂-(2,6-dimethylpiperidine), -SO₂-(2-propylpiperidine), -SO₂-(hydroxypropyl), -C(O)-(2-methoxymethylpyrrolidine), -C(O)-(2-methylpyrrolidine), -C(O)-(2,6-dimethylpyrrolidine), -C(O)-(2-hydroxymethylpyrrolidine), -C(O)N(methyl)(ethyl), -C(O)N(methyl)(propyl), -C(O)N(methyl)(butyl), -C(O)N(propyl)(butyl), -C(O)N(allyl)(cyclopentyl), -C(O)N(allyl)(cyclohexyl), -C(O)N(methyl)(methyl), -C(O)N(ethyl)(ethyl), -C(O)N(butyl)(butyl), -C(O)N(isopropyl)(isopropyl), -C(O)N(propyl)(propyl), -C(O)N(methyl)(cyclohexyl), -C(O)N(ethyl)(cyclohexyl), -C(O)NH(cyclobutyl), -C(O)NH(cyclopentyl), -C(O)N(CH₃)(cyclopentyl), -C(O)NH(2-methylcyclohexyl), -C(O)NH(pentyl), -C(O)N(pentyl)(pentyl), -C(O)NH(isopentyl), -C(O)NH(ethoxyethyl), -C(O)N(CH₃)(methoxyethyl), -C(O)N(propyl)(methoxyethyl),

-C(O)N(methoxyethyl)(methoxyethyl),
 -C(O)N(ethoxyethyl)(ethoxyethyl),
 -C(O)N(ethyl)(methoxyethyl), -C(O)N(propyl)(hydroxyethyl),
 -C(O)N(hydroxyethyl)(ethyl), ethynyl, methyl, bromo,
 5 -N(CH₃)SO₂(CH₃), -N(CH₃)SO₂-thienyl, -
 N(hydroxypropyl)SO₂CH₃, -(CH₂)-SO₂-(CH₃), or -C(O)-
 CH(CH₃)CH₂CH₂CH₃.

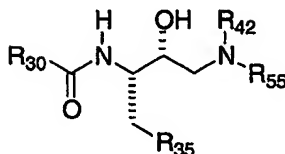
30. A compound according to claim 27 wherein
 10 R₄₀ is phenyl or C₁-C₈ alkyl, wherein each of the above is
 unsubstituted or substituted with 1, 2, or 3 groups that
 are independently halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃,
 -Obenzyl wherein the phenyl is optionally substituted with
 1 or 2 halogens, -CHO, or -NHSO₂-(C₁-C₄ alkyl); and
 15 R₄₁ is hydrogen or C₁-C₆ alkyl optionally substituted with 1 or
 2 groups that are phenyl, hydroxy, or C₁-C₄ thioalkoxy;
 and;
 R₄₂ is hydrogen; and
 R₅₁ at each occurrence is independently C₁-C₆ alkyl, C₁-C₆
 20 alkoxy, -NHSO₂-(C₁-C₄ alkyl) wherein the alkyl group is
 optionally substituted with 1, 2, or 3 halogens, -SO₂-NH-
 (C₁-C₆ alkyl)-NH₂, -SO₂-NH-(C₁-C₆ alkyl)-NH(C₁-C₄ alkyl), -
 SO₂-NH-(C₁-C₆ alkyl)-N(C₁-C₄ alkyl)(C₁-C₄ alkyl),
 -NHC(O)NH₂, -NHC(O)NH(C₁-C₆ alkyl), -NHC(O)N(C₁-C₆
 25 alkyl)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆
 alkyl)C(O)NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)C(O)N(C₁-C₆
 alkyl)(C₁-C₆ alkyl), halogen, -CF₃, OH, -SO₂NR₃₁R₃₂,
 -C(O)NR₃₁R₃₂, -NR₃₁R₃₂, hydroxy C₁-C₁₀ alkyl, -Obenzyl, -
 NHC(S)NH₂, -NHC(S)NH(C₁-C₆ alkyl), -NHC(S)N(C₁-C₆ alkyl)(C₁-
 30 C₆ alkyl), (C₁-C₄ alkyl)-O-phenyl, -C(O)-(C₁-C₆ alkyl), -O-
 cyclopentyl, -O-cyclohexyl, hydroxy C₁-C₄ alkoxy,
 aminoalkoxy, NH(C₁-C₆ alkyl)-alkoxy, N(C₁-C₆ alkyl)(C₁-C₆
 alkyl)-alkoxy,

wherein R_{31} and R_{32} at each occurrence are independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, $-(C_1$ - C_6 alkyl)-NH(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)-N(C_1 - C_6 alkyl)(C_1 - C_6 alkyl), and benzyl wherein the phenyl group is unsubstituted or substituted with 1, or 2 groups that are independently C_1 - C_4 alkoxy, or halogen, wherein at each occurrence R_{31} , R_{32} and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl, each of which is optionally substituted with hydroxy, hydroxy C_1 - C_6 alkyl, C_1 - C_4 alkoxy C_1 - C_6 alkyl, $-C(O)NH_2$, or $-C(O)NH$ -benzyl.

31. A compound according to claim 30 wherein R_{40} is phenyl or C_1 - C_8 alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, or CF_3 ; and R_{51} at each occurrence is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-NHSO_2CH_3$, $-NHSO_2CF_3$, halogen, $-CF_3$, OH, $-SO_2NR_{31}R_{32}$, $-C(O)NR_{31}R_{32}$, $-NR_{31}R_{32}$, hydroxy C_1 - C_{10} alkyl, hydroxy C_1 - C_4 alkoxy, aminoalkoxy, $NH(C_1$ - C_6 alkyl)-alkoxy, $N(C_1$ - C_6 alkyl)(C_1 - C_6 alkyl)-alkoxy, wherein R_{31} and R_{32} at each occurrence are independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, and benzyl wherein the phenyl group is unsubstituted or substituted with 1 or 2 groups that are independently methoxy, ethoxy, or halogen, or wherein at each occurrence R_{31} , R_{32} and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl ring each of which is optionally substituted with hydroxy,

hydroxy C₁-C₆ alkyl, C₁-C₄ alkoxy C₁-C₆ alkyl, or-
C(O)NH₂.

32. A compound of the formula:



5

or a pharmaceutically acceptable salt thereof, wherein

R₃₀ is selected from the group consisting of phenyl,

pyrazolopyrimidinyl, oxa-aza-benzoazulenyl, isoxazolyl,
 triazolopyridinyl, pyrrolidinonyl, tetrahydrothia-aza-
 10 fluorenyl, pyridyl, piperidinyl,
 dihydrocyclopentaquinolinyl, furyl, naphthothienyl,
 phthalazinonyl, thiadiazolyl, thienopyrimidinonyl, oxa-
 diaza-cyclopentanaphthalenyl, dihydrobenzodioxepinyl,
 chromanonyl, chromenonyl, oxazolidinyl, purinyl, oxazolyl,
 15 thiazolyl, pyridazinonyl, thiazolyl, pyranyl,
 dihydropyranopyridinyl, diazepanyl, cyclopropyl,
 dihydronaphthoisoxazolyl, benzoindazole,
 dihydrocyclopentachromenonyl, imidazopyrazolyl,
 tetrahydrocyclopentachromenonyl, dihydroquinolinonyl,
 20 pyridyl, isochromanyl, quinazolinonyl, pyrazolopyridinyl,
 dihydrobenzothiophene dioxide, dihydrofurobenzoisoxazolyl,
 dihydropyrimidine dionyl, thienopyrazolyl, oxazolyl,
 tetrahydrocyclopentapyrazolyl, dihydronaphthalenonyl,
 dihydrobenzofuranonyl, dihydrocyclopentathienyl,
 25 tetrahydrocyclopentapyrazolyl, tetrahydropyrazoloazepinyl,
 indazolyl, tetrahydrocycloheptaisoxazolyl,
 tetrahydroindolonyl, pyrrolidinyl, thienopyridinyl,
 dioxodihydrobenzoisothiazolonyl, triazolopyrimidinyl,
 thienyl, dihydrothienopyrimidinonyl, and benzooxadiazolyl,
 30 wherein each of the above is unsubstituted or substituted
 with 1, 2, 3, 4, or 5 groups that are independently
 selected from the group consisting of

C₁-C₁₀ alkyl optionally substituted with phenyl, hydroxy,
 hydroxy C₁-C₁₀ alkyl optionally substituted with
 phenyl or (C₁-C₄ alkyl)phenyl, C₁-C₆ alkoxy optionally
 substituted with 1 or 2 hydroxy groups, -C(O)NR₃₁R₃₂,
 5 -NR₃₁-SO₂-(C₁-C₆ alkyl) wherein the alkyl group is
 optionally substituted with 1, 2, or 3 R₃₃ groups, -
 SO₂-NH(C₁-C₆ alkyl) wherein the alkyl group is
 optionally substituted with 1 or 2 R₃₃ groups, -SO₂-
 N(C₁-C₆ alkyl)(C₁-C₆ alkyl) wherein each alkyl group
 10 is optionally substituted with 1 or 2 R₃₃ groups, -
 SO₂-NH(C₁-C₆ alkyl)-phenyl wherein the phenyl is
 optionally substituted with 1 or 2 groups that are
 independently C₁-C₄ alkoxy or halogen, -O-(C₁-C₆
 alkyl)-phenyl, -(C₁-C₆ alkyl)-O-phenyl, -(C₁-C₆
 15 alkyl)-O-(C₁-C₆ alkyl)-phenyl, triazolidine-3,5-
 dione, halogen, -NHC(O)NH₂, -N(C₁-C₆ alkyl)C(O)NH₂,
 -N(C₁-C₆ alkyl)C(O)NH(C₁-C₆ alkyl), -N(C₁-C₆
 alkyl)C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)
 thienyl, -(C₁-C₆ alkyl) furanyl, -S-(C₁-C₆ alkyl)
 20 phenyl, -SO₂NR₃₁R₃₂, -C(O) -NR₃₁R₃₂, -NR₃₁R₃₂, dithiane,
 -NHC(S)NH₂, -NHC(S)NH(C₁-C₆ alkyl), -NHC(S)N(C₁-C₆
 alkyl)(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl),
 tetrahydropyran, phenyl optionally substituted with 1
 or 2 groups that are independently F, Cl or Br,
 25 pyridine, -C₂-C₄ alkynyl-phenyl, -O-C₃-C₆ cycloalkyl,
 -O-(C₁-C₆ alkyl)-R₃₃, benzo[1,2,5]oxadiazole, -C(O)-
 (C₁-C₆ alkyl) wherein the alkyl group is optionally
 substituted with NH₂, N(C₁-C₆ alkyl), or N(C₁-C₆
 alkyl)(C₁-C₆ alkyl); -C(O)NH-phenyl, -C(O)N(C₁-C₆
 30 alkyl)-phenyl, 4,4-Dimethyl-4,5-dihydro-oxazole, -
 (C₁-C₆ alkyl)-S-pyridine, -(C₁-C₆ alkyl)-SO₂-pyridine,
 -(C₁-C₆ thioalkoxy)-pyridine,
 wherein R₃₁ and R₃₂ at each occurrence are independently
 selected from the group consisting of hydrogen, C₁-C₆